PHD

Palladium-catalysed C--X bond formations

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Palladium-Catalysed *C-X* Bond Formations

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Department of Chemistry

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This work was carried out in collaboration with Pfizer as part of a CASE studentship.

Supervisors: Dr Michael C. Willis, University of Bath
Dr Adam T. Gillmore, Pfizer

Abstract

Over the last decade palladium catalysed *C-X* cross-coupling reactions have been developed successfully as a major tool for the synthetic chemist (**Chapter 1**) and our contribution to this key area of research will be detailed herein.

Chapter 2 describes our successful application of palladium catalysis to the formation of new *C-O* bonds in the synthesis of aryl enol ethers. Vinyl triflates can be efficiently converted into the corresponding aryl enol ethers by treatment with a phenol, NaO^tBu and a catalyst generated from $Pd_2(dba)_3$ and 2-(di-*tert*-butylphosphino)biphenyl **3b**. Palladium catalysed vinylic *C-O* bond formation is the key-step in efficient preparation of a range of substituted aryl enol ethers.[1]

Chapter 3 introduces the protocol we have investigated towards the application of palladium catalysed *C-O* bond formations to the synthesis of the benzofuran motif. A catalyst generated from $Pd_2(dba)_3$ and DPEphos effects intramolecular *C-O* bond formation between enolates and aryl halides in the conversion of 1-(2-haloaryl)ketones directly into the corresponding benzofurans. Both cyclic and acyclic ketones are efficient substrates. Thio-ketones can also be employed, allowing the preparation of the corresponding benzothiophenes.[2]

Chapter 4 presents our approach towards a novel cascade *O*-annulation route to the benzofuran motif, establishing a double palladium catalysed *C-O* bond forming cross-coupling reaction. A catalyst generated from $Pd_2(dba)_3$ and 2-(di-*tert*-butylphosphino)biphenyl **3b** in the presence of sodium trimethylsilanoate, acting as both an oxygen donor and base, effects an unusual tandem *C-O* bond formation involving an intermolecular alkenyl *C-O* bond formation with subsequent aryl *C-O* bond formation. The identical reaction can also be achieved in a competitive yield employing a catalyst generated from $Pd_2(dba)_3$ and $HP^tBu_3BF_4$ in the presence of the mild base Cs_2CO_3 and 2-tosylethanol as the oxygen donor.

Chapter 5 reports the palladium catalysed intramolecular aryl enol ether synthesis from vinyl triflates. Our established catalyst generated from $Pd_2(dba)_3$ and DPEphos with the mild base Cs_2CO_3 successfully executes the intramolecular cyclisation of a phenolic oxygen onto an adjacent vinyl triflate group to give the corresponding benzofuran in excellent yield. The analogous thiol cross-coupling reaction can also be achieved to give the corresponding benzothiophene in excellent yield. Preliminary studies towards the

expansion of our *O*-enolate cyclisation strategy, mentioned earlier, for the formation of six membered ring aryl enol ethers were successful.

Chapter 6 gives overall conclusions and outlines the continuing and future work being carried out in this area.

Chapter 7 is a formal account of experimental procedures.

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Contents

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To those doctors/marrieds/wanabes with whom I shared a lab, it has been a pleasure to work with you all especially the girlies Rach, Gan and Ana.

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Finally, my family, my surrogate family, my friends and Davy.

Abbreviations and Acronyms

Å	Angstrom
Ac	acetyl
acac	acetyl acetate
app.	apparent
aq.	aqueous
Ar	aryl
BINAP	2,2'-*bis*-(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	n-butyl
^{t}Bu	*tert*-butyl
°C	degrees celcius
CI	chemical ionisation
COD	cyclooctadienyl
conv.	conversion
Cp	cyclopentadienyl
C_S	element of symmetry
Cy	cyclohexyl
d	doublet
δ	chemical shift in parts per million
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
dba	dibenzylideneacetone
dbpf	1,1'-*bis*(di-*tert*-butylphosphino)ferrocene
DCM	dichloromethane
de	diastereomeric excess
dioxane	1,4-dioxane
DMA	dimethylamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	dimethylaminopyridine

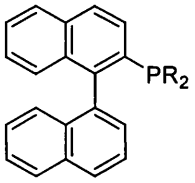
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMFDMA	*N,N*-dimethylformamide dimethyl acetal
DMPS	dimethylphenylsilyl
DMPSE	(dimethylphenylsilyl)ethyl
DMSO	dimethylsulfoxide
DPEphos	bis-(2-diphenylphosphinophenyl) ether
DPP	4,7-diphenyl-1,10-phenanthroline
dppbz	diphenylphoshinobenzene
dppe	diphenylphosphinoethane
d^{i}ppf	1,1'-*bis*(di-*iso*-propylphosphino)ferrocene
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dppp	diphenylphoshinopropane
dtpf	1,1'-*bis*(di-*o*-tolylphosphino)ferrocene
DYKAT	dynamic kinetic asymmetric transformation
ed.	edited by
ee	enantiomeric excess
EI	Electron Impact
eq.	equivalent
ES	Electrospray
Et	ethyl
g	gram
h	hour
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
i	*iso*, equal
J	coupling constant (in NMR spectroscopy)
L	ligand
L*	chiral ligand
LDA	lithiumdi*iso*propylamide
M	molar (number of moles per litre)
m	multiplet
m-	meta

m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	Megahertz
min.	minute(s)
mL	millilitre
mmol	millimole
MOM	methoxymethyl
mp	melting point
MS	molecular sieves
mw	microwave
m/z	mass to charge ratio
n	normal
NBS	*N*-bromosuccinimide
NMP	*N*-methyl pyrrolidine
NMR	Nuclear Magnetic Resonance Spectroscopy
o-	ortho
Oct	octyl
p-	para
Ph	phenyl
PG	protecting group
PPA	polyphosphoric acid
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	*n*-propyl
^{i}Pr	*iso*-propyl
PTSA	*para*-toluenesulfonic acid
q	quartet
R	general hydrocarbon substituent
rac	racemic
RCM	Ring Closing Metathesis
rt	room temperature
s	singlet
sec	secondary

SEM	methoxyethyltrimethylsilane
Semi-ESPHOS	1-(2-methoxyphenyl)-2-phenylhexahydropyrrolo[1,2-*c*][1,3,2]diaza-phosphole
sept.	septet
S-phos	2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl
t	triplet
t or *tert*	tertiary
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPSE	(*tert*-butyldiphenylsilyl)ethyl
TBHP	*tert*-butyl hydroperoxide
TBS	tri-*tert*-butylsilyl
TES	triethylsilyl
Tf or triflate	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFP	tetrafluorophenol
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TMSE	(trimethylsilyl)ethyl
Tol	tolyl
TPS	triphenylsilyl
Ts	*para*-toluenesulfonyl (tosyl)
TS	transition state
Vanillin	4-hydroxy-3-methoxybenzaldehyde
X	general halide substituent, heteroatom
X-phos	2-(dicyclohexylphosphino)-2',4',6'-tri*iso*propyl-1,1'-biphenyl
υ	Frequency

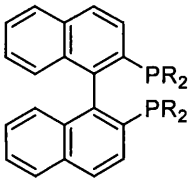
Ligands[1-5]

Naphthyl-based ligands



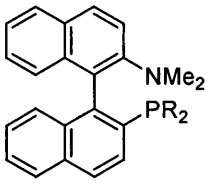
1a: **R=Cy**: dicyclohexyl-phosphinobinaphthyl

1b: **R=^{t}Bu**: di-*tert*-butyl-phosphinobinaphthyl



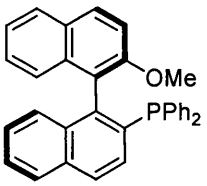
(***rac*)-BINAP**: **R=Ph**: *rac*-2,2'-*bis*-(diphenylphosphino)-1,1'-binaphthyl

Tol-BINAP: **R=(o-Tol)**: *rac*-2,2'-*bis*-(di-*p*-tolylphosphino)-1,1'-binaphthyl



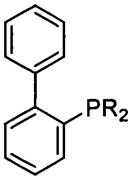
2a: **R=Cy**: (2'-dicyclohexylphos-phino-[1,1']-binaphthalenyl-2-yl)-dimethylamine

2b: **R=^{t}Bu**: (2'-di-*tert*-butylphos-phino-[1,1']binaphthalenyl-2-yl)-dimethylamine



MeO-MOP: (2'-methoxy-[1,1']binaphthalenyl-2-yl)-diphenylphosphane

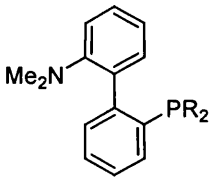
Biphenyl-based ligands[6]



3a: **R=Cy**: 2-(dicyclohexylphos-phino)-biphenyl

3b: **R=^{t}Bu**: 2-(di-*tert*-butylphos-phino)-biphenyl

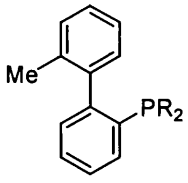
3c: **R=Ph**: 2-(di-phenylphos-phino)-biphenyl



4a: **R=Cy**: **Dave-phos**; 2-(dicyclo-hexylphosphino)-(*N,N*-dimethyl-amino)biphenyl

4b: **R=^{t}Bu**: 2-(di-*tert*-butylphos-phino)-(*N,N*-dimethylamino)-biphenyl

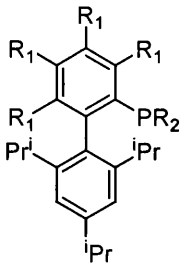
4c: **R=Ph**: 2-(di-phenylphos-phino)-(*N,N*-dimethylamino)-biphenyl



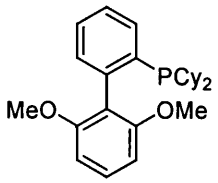
5a: **R=Cy**: 2-(dicyclohexylphos-phino)-2'-methylbiphenyl

5b: **R=^{t}Bu**: 2-(di-*tert*-butylphos-phino)-2'-methylbiphenyl

5c: **R=Ph**: 2-(diphenylphos-phino)-2'-methylbiphenyl



X-phos: R_1=H, R=Cy: 2-(dicyclohexylphosphino)-2',4',6'-tri*iso*-propyl-1,1'-biphenyl

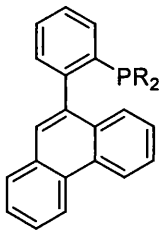


S-phos: 2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl

***tert*-Butyl X-Phos**: R_1=H, R=^{t}Bu: 2-(di-*tert*-butylphosphino)-2',4',6'-tri*iso*propyl-1,1'-biphenyl

R_1=Me, R=^{t}Bu: 2-(di-*tert*-butylphosphino)-3,4,5,6-tetramethyl-2',4',6'-tri*iso*propyl-1,1'-biphenyl

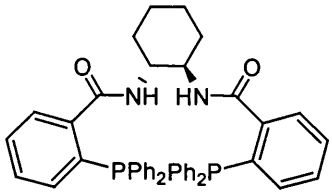
Aryl-based ligands[7]



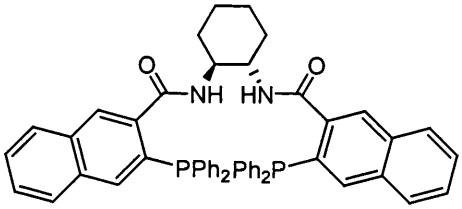
6a: R=Cy: dicyclohexyl-(2-phenanthren-9-yl-phenyl)-phosphane

6b: R=^{t}Bu: di-*tert*-butyl-(2-phenanthren-9-yl-phenyl)-phosphane

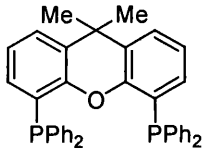
6c: R=Ph: diphenyl-(2-phenanthren-9-yl-phenyl)-phosphane



7a: **Salen derivative**:[8] (+)-1,2-*bis*-*N*-[2'-(diphenylphosphino)benzoyl]-1(*R*),2(*R*)-diaminocyclohexane

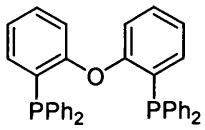


7b: **Naphthyl derivative**: (-)-1,2-*bis*-*N*-[2'-(diphenylphosphino)naphthamido]-1(*S*),2(*S*)-cyclohexane



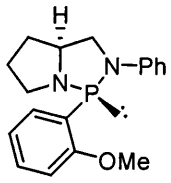
Xantphos[9]

4,5-*bis*-(diphenylphosphino)-9,9-dimethylxanthene

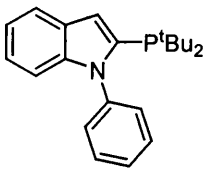


DPEphos[10]

bis-(2-diphenylphosphinophenyl) ether

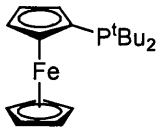


Semi-ESPHOS: 1-(2-methoxyphenyl)-2-phenyl-hexahydropyrrolo[1,2-*c*][1,3,2]diazaphosphole

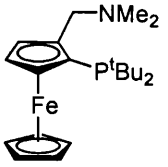


8: 2-(di-*tert*-butylphosphino)-*N*-phenylindole

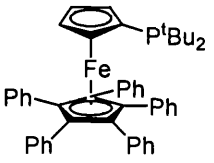
Ferrocene-based ligands[11-13]



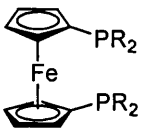
9: Di-*tert*-butylphosphino-ferrocene



10: 2-[(dimethylamino)methyl] di-*tert*-butylphosphinoferrocene



11: 1-Di-*tert*-butylphosphino-1',2',3',4',5'pentaphenylferrocene



12a: **d^{i}ppf**; **R=^{i}Pr**: 1,1'-*bis*(di-*iso*-propylphosphino)ferrocene

12b: **d^{t}bpf**; **R=^{t}Bu**: 1,1'-*bis*(di-*tert*-butylphosphino)ferrocene

12c: **dppf**; **R=Ph**: 1,1'-*bis*(diphenylphosphino)ferrocene

12d: **dtpf**; **R=*o*-Tol**: 1,1'-*bis*(di-*o*-tolylphosphino)ferrocene

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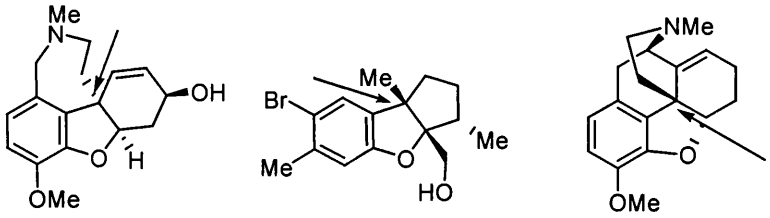
Chapter 1 Introduction

1.1 Investigation aims

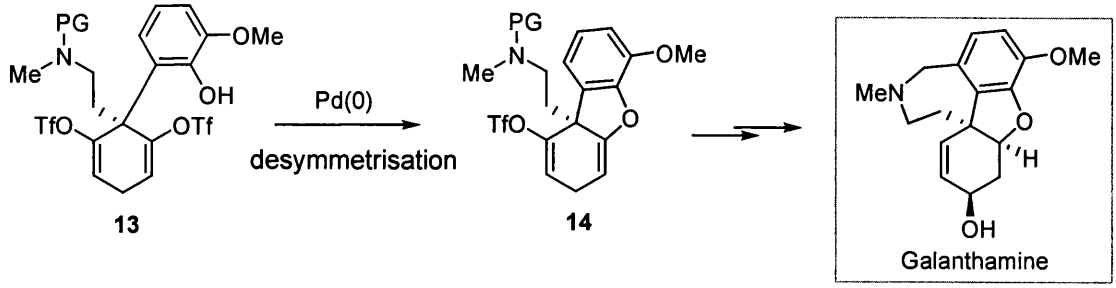
The efficient and stereoselective synthesis of quaternary carbon centres remains a formidable challenge to the synthetic chemist and many biologically important designs encompass these motifs. **Figure 1.1** depicts two such target compounds containing a quaternary chiral centre, as indicated. Other key features of this class of compounds include the common aryl subunit adjacent to the chiral centre and the hetero-substituted stereocentre that is incorporated into the heterocyclic ring system. A new catalytic enantioselective strategy for their synthesis employing palladium catalysis will be described herein. Crucially, although an enantioselective desymmetrisation strategy using palladium catalysis will be employed, the methods lead to products containing *stereochemically defined carbon atoms* and not chiral planes or chiral axes.



galanthamine **aplysinol** **desoxycodiene**

Figure 1.1 Naturally occurring chiral dihydrobenzofurans

One possible pathway towards the synthesis of the acetylcholinesterase inhibitor galanthamine employs an enantioselective palladium catalysed *etherification* reaction as the key step (**Scheme 1.1**). The symmetrical *bis*-vinyl triflate **13** can be readily prepared from a diketone, an aryl bromide and an activated amine. An intramolecular desymmetrising *etherification* reaction would generate the aryl enol ether derivative **14**. Advancement through triflate reduction, enol ether reduction, deprotection and finally, a series of known steps would give the desired product. The key intramolecular etherification between a vinyl triflate or -halide and an alkoxide nucleophile has, to our knowledge, not been reported in the literature and it was this reaction we wished to investigate and exploit.



Scheme 1.1 Galanthamine part synthesis

1.2 Desymmetrisation[1]

Desymmetrisation methodology is fundamental to the success of our investigation. The reactant molecule has C_s symmetry with a mirror plane passing through the centre, resulting in two enantiotopic triflate groups (**Figure 1.2**). One face is more sterically hindered than the other as a direct result of the size of the attached groups at the quaternary centre on the ring-system. The least hindered face is then more accessible and susceptible to the approach of a sterically bulky catalyst, thus, discriminating *via* enantiotopic group selection.

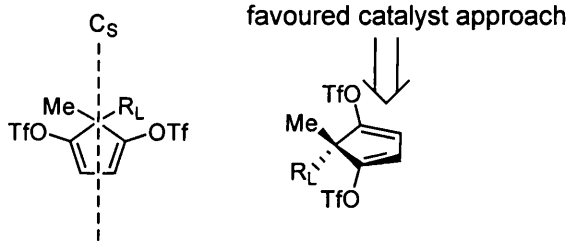


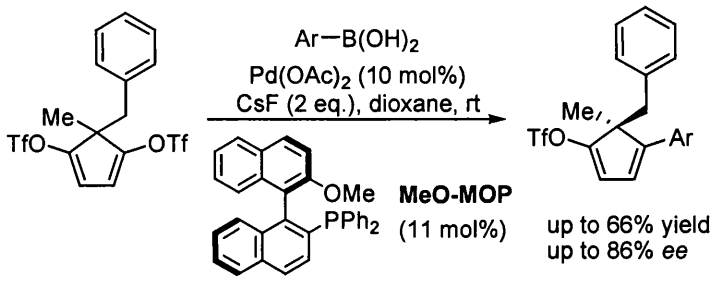
Figure 1.2 Principals of the desymmetrisation process

There will no longer be a mirror plane passing through the molecule upon palladium-catalysed substitution at only one of the vinyl triflate active sites. The quaternary centre has become a chiral centre and diastereomers are generated due to the chiral ligand. If one diastereomer reacts more rapidly, then desymmetrisation will occur.

1.3 Recent Results from our Laboratory

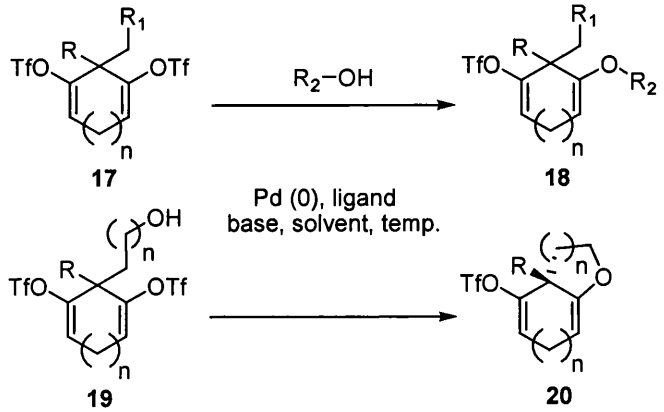
Recent studies within the Willis group have demonstrated that palladium catalysed cross couplings can be employed as effective desymmetrising reactions.[2,3,4] Enantioselective intermolecular palladium catalysed *C-C* bond formations have been executed with success on symmetrical *bis*-vinyl triflates **15** employing Suzuki methodology. The incorporation of a hemilabile chiral ligand such as MeO-MOP has afforded impressive

enantioselectivities (**Scheme 1.2**). These initial results were an encouraging first venture worthy of extension to *C-X* bond formations.



Scheme 1.2 *Bis*-vinyl triflate desymmetrisation

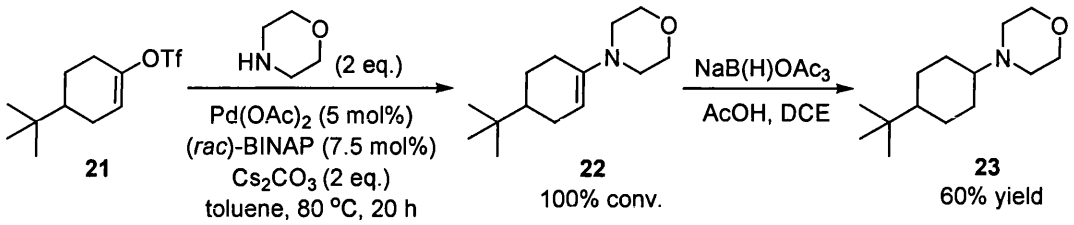
Our primary studies will focus on the analogous palladium catalysed *C-O* bond formations. First, preliminary reactions must be carried out to determine the feasibility of the *C-O* variant and to establish general palladium catalytic conditions for the intermolecular cross-coupling reaction between more simple mono-vinyl triflates and substituted phenol derivatives. Eventually, following its success, the reaction will be evaluated against *bis*-vinyl triflates **17**, intermolecularly. Once established, the system will be evaluated intramolecularly (**Scheme 1.3**). We plan to use a range of symmetrical *bis*-vinyl triflates **19** that carry nucleophilic oxygens attached to the central carbon atom *via* either a saturated or aryl tethering group. The analogous *C-S* bond formation studies will be carried out in conjunction with the *C-O* studies.



Scheme 1.3 Proposed palladium catalysed *C-O* bond forming desymmetrisation reactions

Scheme 1.4 depicts the key system established in the Willis laboratory by Brace for the formation of enamines **22** in excellent conversions from simple mono-vinyl triflates **21** and amines.[5] The scope of this process with respect to amine structure has been evaluated with great success,[6] although reduction of the reactive enamines *in-situ* to generate the more stable amines **23** was required in some cases for quantitative analysis.

The group of Wallace has also reported the amidation of a range of enol triflates employing a catalyst generated from $Pd_2(dba)_3$ and Xantphos in the presence of the weak base Cs_2CO_3 at the milder temperature of 50 °C in dioxane in excellent yields.[7] The analogous enol ether syntheses have been investigated and the results will be discussed below.



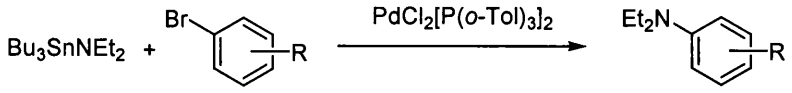
Scheme 1.4 Palladium catalysed synthesis of enamines from vinyl triflates

The proposed methodology presents a new approach to the development of enantioselective palladium-catalysed coupling reactions, establishing new protocols for *C-O* and *C-S* bond formations. These reactions will eventually be developed as the key bond construction for the formation of enantiomerically enriched chiral building blocks to be used in organic synthesis.

1.4 Palladium Catalysis: *C-X* Bond Formations

Palladium has proven to be one of the most versatile and useful of the transition metals used for organic synthesis. The scope of *C-C* bond formations has increased significantly over the past 30-40 years with advances in Heck,[8-11] Kumada (RMgX),[12] Negishi (R_2Zn),[13-15] Stille ($RSnR'_3$),[16-18] Suzuki-Miyaura ($RB(OR')_2$)[19-22] and Sonogashira (RCuX)[23-28] cross-coupling reactions.[29-32] A recent review by Tietze, Ila and Bell provides the reader with a comprehensive overview of the ever expanding area of enantioselective palladium-catalysed transformations.[33] However, some of the most significant advances over the last decade have been made in the area of *C-X* bond formations with major contributions from the Buchwald and Hartwig groups.[34,35]

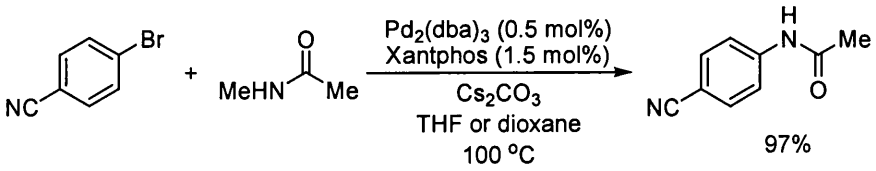
Previously, in 1983, Kosugi *et al.* described a modified Stille-type cross-coupling reaction of tributyltin amides with aryl bromides catalysed by $PdCl_2[P(o\text{-}Tol)_3]_2$ (**Scheme 1.5**).[36,37] Unfortunately, the scope of the reaction was limited to dialkylamides and electron-neutral aryl bromides. The use of vinyl bromides resulted in modest yields of enamines in some cases.



Scheme 1.5 Early palladium catalysed *C-N* bond formation

It was not until the early 1990s that this methodology was developed further by several groups to encompass a wider range of substrates.[38-41] Eventually, in 1995 the groups of Buchwald[41] and Hartwig[42] reported simultaneously their work on 'tin-free' aminations of aryl halides. The reactions were conducted by reaction of an aryl halide with the combination of a free amine in the presence of a palladium catalyst [$Pd_2(dba)_3$, P(o-Tol)$_3$] and an alkoxide or silylamide base. They also found that running the reaction in dioxane as solvent was necessary to obtain even modest yields. Since this discovery there has been an explosion of interest in this area with several comprehensive reviews demonstrating its importance.[34,43-45]

The cross coupling of aryl halides,[46] triflates,[47] tosylates and nonaflates (-$OSO_2(CF_2)_3CF_3$)[48] or vinyl halides[49,50] and triflates[7] with primary amines, both acyclic or cyclic secondary or tertiary amines as well as amides, sulfonamides, carbamates and imines both inter- and intramolecularly to give the corresponding substituted amines are only some of the reactions that have been successful. **Scheme 1.6** depicts one such example by Yin and Buchwald employing a catalyst generated from $Pd_2(dba)_3$ and Xantphos to affect the cross-coupling reaction between aryl bromides and amides.[51] They found that in the presence of a weak base, Cs_2CO_3, aryl bromides possessing electron-withdrawing and electron-neutral groups could be effectively coupled with both primary and secondary amides.

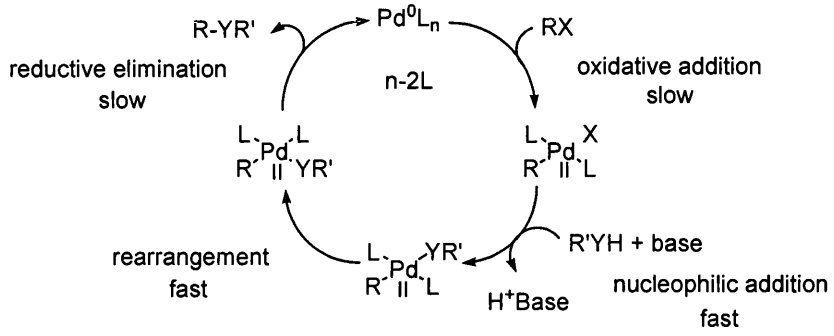


Scheme 1.6 Synthesis of arylamides from aryl halides

Palladium-catalysed *C-N* bond formations have found great use in the formation of naturally occurring polyheterocycle scaffolds[52,53] including indoles,[54-57] carbazoles,[58] quinolines and naphthyridinones.[59] This report will focus upon the palladium catalysed *C-O* and *C-S* bond forming reactions that have naturally progressed from the analogous *C-N* bond forming reactions.

1.5 General Catalytic Cycle

Scheme 1.7 depicts the general palladium catalytic cycle for *C-X* bond formations. First, oxidative addition of a molecule RX to an unsaturated Pd(0) species results in the formation of two new bonds R-Pd-X. Effectively Pd(0) is oxidised to Pd(II). In general, the rate of addition is modified by the nature of the substituent in the following manner: *C-I* > *C-OTf* ≥ *C-Br* >> *C-Cl* >> *C-F*. This oxidative addition step can be rate-determining, although, the rate can be enhanced by increasing the electron-donating ability of the ligands used.



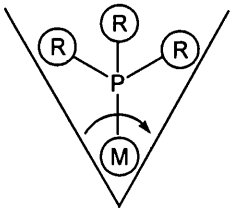
Scheme 1.7 Palladium catalytic cycle

The next stage in the cycle for *C-C* bond formations involves the transfer of an alkyl, aryl or hydrogen from a more electropositive metal to the palladium, substituting the best leaving group of the palladium complex, usually a halide ion. This step is called the alkylation of palladium or, better known as, transmetallation and is generally the rate-determining step of the cycle. The metal can be chosen from a variety of main group and transition group metals *eg.* Zn, B, Al, Sn, Si, Hg. Transmetallation also occurs with retention of any stereochemistry in the migrating organic group. For *C-X* bond formations this step is replaced with a *pseudo*-transmetallation or a nucleophilic substitution reaction. Usually a base is employed to deprotonate the nucleophilic species either prior to, or following, co-ordination at the palladium centre and also to assist the removal of the halide-leaving group. The order of events is ambiguous and is typically substrate dependant.

Regeneration of the Pd(0) species for subsequent repetition of the cycle occurs upon reductive elimination to liberate the product *via* the coupling and elimination of two one-electron ligands of *cis* configuration with respect to the palladium. The *cis* configuration is maintained throughout the cycle when a bidentate ligand is operative, otherwise a fast ligand rearrangement step is required. The palladium is effectively reduced from Pd(II)→Pd(0).

β-Hydride elimination is a common side reaction, generating an unsaturated species from an organopalladium complex *via syn*-elimination of a *β*-hydride. Formation of a five co-ordinate intermediate species is thought to occur prior to elimination when both the unsaturated species and hydride are co-ordinated to the palladium simultaneously. As a result, an unsaturated palladium complex is required (a complex with fewer than 18 bonding electrons). This step can occur very rapidly, even at temperatures as low as –20 °C.

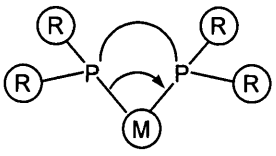
The ratio of products obtained from either reductive elimination or *β*-hydride elimination can be controlled, to a certain extent, by the choice of ligand. The reductive elimination step for *C-O* bond formations is deemed the rate-limiting step and it has been shown that the rate of elimination can be improved by increasing the steric bulk of the ligand. Oxidative addition can also be affected. The relative 'bulk' of a monodentate phosphine ligand can be estimated by the measure of its 'cone angle' (**Figure 1.3**). The diversity of ligand bulk is shown by comparison of simple phosphine ligands. As a consequence, it is possible to fine-tune this angle by modification of the ligand and hence alter the reactivity of the catalyst.



ligand	$P(OEt_3)$	$P(O\text{-}p\text{-}Tol)_3$	$P(O\text{-}o\text{-}Tol)_3$	PPh_3	PCy_3	P^tBu_3
cone angle (°)	109	128	141	145	170	182

Figure 1.3 Phosphorus 'cone angle' as a measure of ligand bulk[60]

The relative bulk of a bidentate or polydentate ligand can be estimated by the measure of its 'bite angle' (**Figure 1.4**).[61,62] The P-M-P bite angle depends on the flexibility of the ligand backbone and the bulk of the attached phosphine groups. The values given in **Figure 1.4** were calculated from models and are only a rough guide to the chemist. Some ligands can be either *cis* or *trans*-chelating in the metal complex, altering the observed bite angle. For example, Buchwald reported the *trans*-chelating ability of Xantphos, isolating an organopalladium complex with a bite angle >150° (*cf. cis* 97-133°).[63]



ligand	dppe	BINAP	dppf	DPEphos	Xantphos
bite angle (°)	78	92 (89-95)	96 (92-100)	102 (86-120)	111 (97-133)

Bite angles were calculated from models or from X-ray crystallography (the range of bite angles a ligand can accomodate within a 3 kcalmol^{-1} energy barrier)

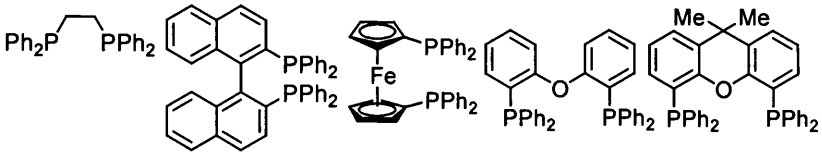


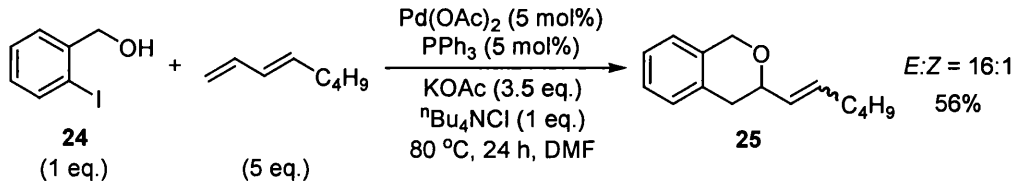
Figure 1.4 Phosphorus 'bite angle' as a measure of ligand bulk[62]

The following two sections will give a brief outline of several of the more important types of palladium catalysed *C-O* bond formations reported in the literature. The reactions that have the most relevance to and the most influence on our work will be discussed in more detail throughout the remainder of this report.

1.6 Palladium Catalysed Intermolecular *C-O* Bond Formations

A review in 1999 by Larock summarised the use of palladium catalysis in heteroannulation processes including the annulation of cyclic and bicyclic alkenes, unsaturated cycloalkanes, allenes, dienes and internal alkynes by substituted aryl and vinylic halides and triflates.[64] The group of Larock have themselves contributed greatly to this area of palladium catalysis from as early as the 1980's.

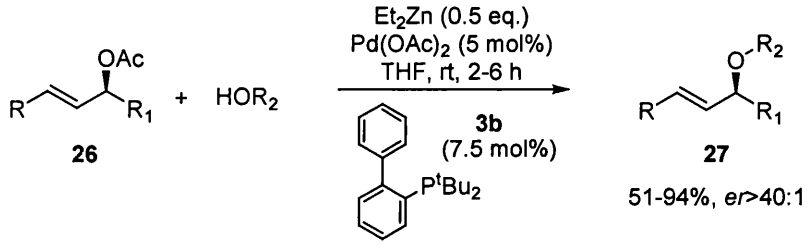
They first reported the palladium-promoted reaction of functionalised aryl or vinylic mercurials with 1,3- and 1,4-dienes, as well as vinylic cyclopropanes, followed by base promoted cyclisation of the initially formed π-allylpalladium intermediates.[65,66] Later, in 1990 they reported the formation of a variety of oxygen containing heterocycles **25** by palladium catalysed coupling of hetero-atom containing aryl iodides **24** with a range of 1,3-dienes (**Scheme 1.8**).[67] A catalyst generated from either $Pd(OAc)_2$ or $Pd(dba)_2$ and PPh_3 in the presence of either NaOAc, KOAc or Na_2CO_3 as base was deemed the most effective. Benzyl alcohols possessing electron-withdrawing groups generally afforded higher yields, with sensitive functional groups such as aldehydes and ketones being tolerated.



24 (1 eq.) (5 eq.) **25**

Scheme 1.8 Palladium catalysed heteroannulation of 1,3-dienes

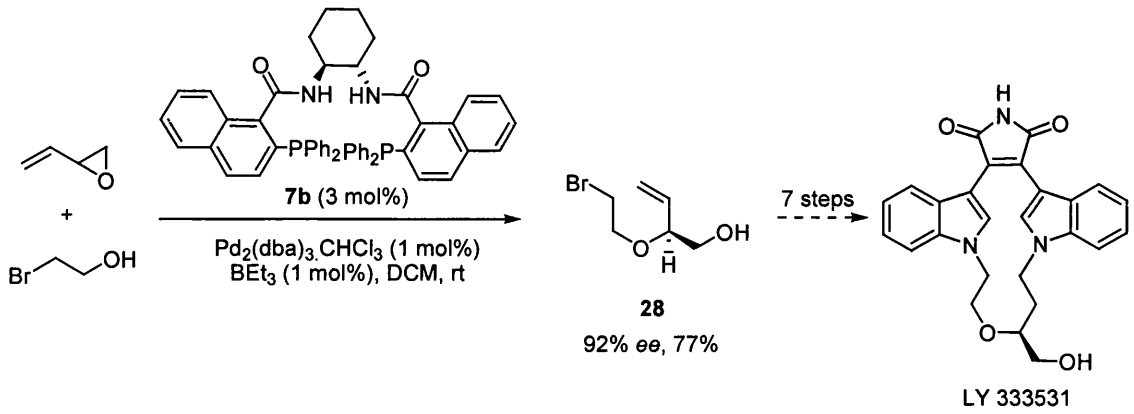
Kim and Lee have realised both a chemo- and stereoselective palladium catalysed allylic etherification reaction between an allylic acetate **26** and an aliphatic alcohol to give a substituted allylic ether **27** (**Scheme 1.9**).[68] The reaction is only successful when an auxiliary source of zinc(II) is added. The highly basic nature of the alkoxide anion is often a virtue for S_N2 type *O*-alkylations when inversion of stereochemistry is desired, also, displacements with alkoxide nucleophiles at stereogenic centers are prone to elimination and loss of stereochemical integrity. The zinc acts as a suppressor of basicity as it binds to the alkoxide anion, softening the nucleophile and modifying its compatibility towards the soft Pd-bound allylic cation. Only 0.5 equivalents of diethyl zinc are required with 5 mol% $Pd(OAc)_2$ and 7.5 mol% of a biphenylphosphino ligand **3b** at ambient temperature. As a result of these mild conditions a variety of acyclic and cyclic substrates participate in inter- and intramolecular allylic etherifications. Previous work by Organ and Miller described an analogous reaction between an allyl bromide and a phenoxide nucleophile in the presence of the commercially available catalyst $Pd(PPh_3)_4$ to give the corresponding allyl aryl ether.[69]



Scheme 1.9 Stereoselective formation of *C-O* bonds

A review by Trost and Crawley in 2003 highlighted the contributions, mainly from the Trost group, in the area of asymmetric transition-metal-catalysed allylic alkylations and its applications in total synthesis with specific interest in the use of palladium catalysis.[70] They describe several key palladium-catalysed asymmetric *C-O* bond formations employing oxygen nucleophiles, such as primary alcohols, carboxylates and phenols. One example given describes the employment of a palladium-catalysed asymmetric allylic alkylation reaction between an allylic epoxide and an alcohol to set the key stereogenic centre of a principal substrate towards the synthesis of Lilly drug LY 333531, a selective protein kinase C inhibitor (**Scheme 1.10**).[71] The epoxide, butadiene monoepoxide was reacted with commercially available 2-bromoethanol in the presence of a palladium catalyst generated from $Pd_2(dba)_3.CHCl_3$ and the Trost naphthyl ligand **7b** in a dynamic kinetic asymmetric transformation (DYKAT) to afford the *bis*-alkylating agent **28** in both excellent yield and *ee*. The choice of ligand is

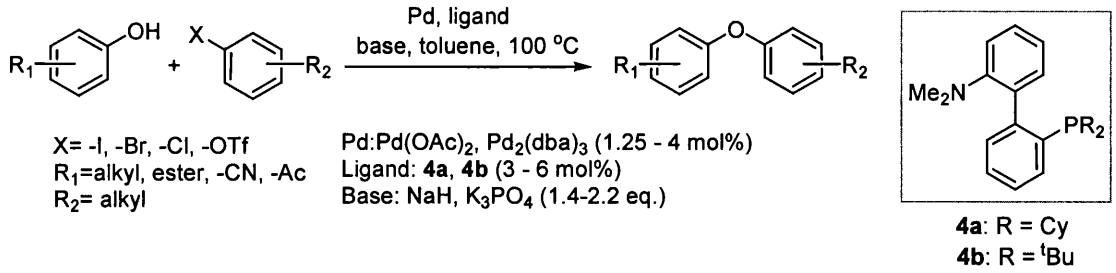
integral to the efficiency and stereoselectivity of the reaction. The tightening of the chiral pocket slows the rate of nucleophilic attack, subsequently increasing both the regio- and enantioselectivity of the reaction by ensuring full equilibration of the intermediate diastereomeric complexes. This intermediate is transformed in 7 steps to the desired product (LY 333531).



Scheme 1.10 Palladium catalysed asymmetric allylic alkylation

A complimentary series of reviews by Muzart give a comprehensive overview of the literature surrounding palladium-catalysed reactions of alcohols[72-74] and in particular the formation of allylic ether linkages.[75] He reviews both the inter- and intramolecular addition of alcohols to η^3-allylpalladium intermediates derived from a variety of substituted allyl moieties including allylic alcohols, vinyl epoxides, alkylidene cyclopropanes, allylic chlorides, allylsilanes, alkenes, alkynes and 1,2- or 1,3-dienes.

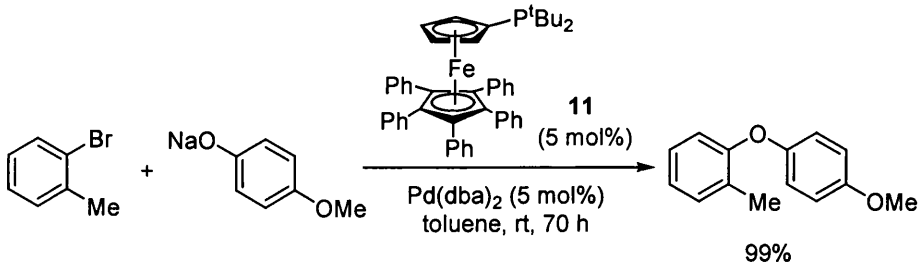
The preparation of diaryl ethers can also be performed through reductive elimination of arylpalladium phenoxides which can be easily prepared from electron-deficient, electron-neutral and electron-rich aryl halides or sulfonates with phenols in the presence of a palladium catalyst and base (**Scheme 1.11**).[76] The reaction has been achieved with strong base, in toluene at elevated temperatures. The use of electron-rich phosphine ligands **4a** and **4b** accelerates the oxidative addition of palladium to aryl chlorides, giving enhanced scope to the reaction. As the rate-determining step, reductive elimination can be enhanced by increasing the steric bulk of the dialkyl side groups on the backbone of the biphenylphosphino ligand.



Scheme 1.11 Diaryl ether synthesis

The arylation of aliphatic alcohols was found particularly challenging prior to the generation of these new palladium catalyst systems due to the competitive *β*-hydride elimination side reaction that had been deemed more prevalent for *C-O* bond formations than for *C-N* bond formations. The alkyl aryl ether synthesis was affected under essentially the same conditions, substituting the biphenylphosphino ligand for *rac*-2,2'-*bis*(di-*p*-tolylphosphino)-1,1'-binaphthyl (Tol-BINAP) ligand.[77] Yields of greater than 50% were attained. However, for aryl bromides containing electron-withdrawing substituents the uncatalysed reactions in DMF gave competitive yields. Polar aprotic solvents enhance the rates of nucleophilic aromatic substitution processes and electron-withdrawing substituents enhance the electrophilicity of the aryl bromide, in turn, increasing the overall rate of reaction.

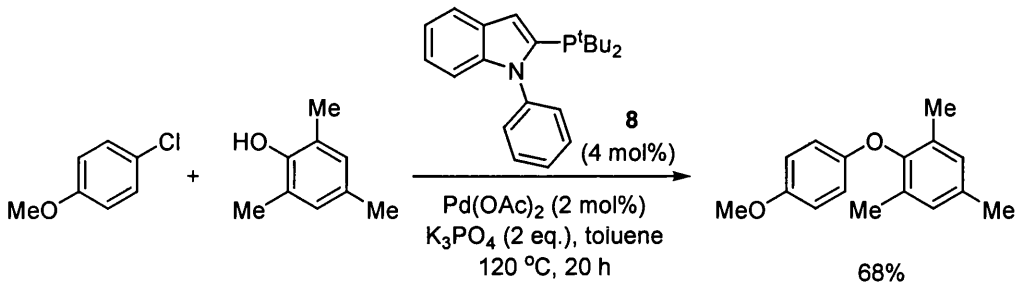
Subsequent reports in the literature provide milder, more efficient catalyst combinations that successfully execute the cross coupling of a wider range of substrates. Hartwig detailed the facile formation of both diaryl ethers and mixed alkyl aryl ethers at room temperature in the presence of a catalyst generated from $Pd(dba)_2$ and the ferrocenyl based ligand **11** (**Scheme 1.12**).[78]



Scheme 1.12 Room temperature palladium catalysed aromatic *C-O* bond formations

More recently, the group of Beller reported the diaryl ether synthesis from aryl chlorides and phenols employing novel indole based ligands **8** (**Scheme 1.13**).[79] In general, they found that an increase in bulk of the electron-rich ligand facilitates the coupling reaction, consistent with previous observations. Both *tert*-butyl and 1-adamantyl groups on the phosphorus gave positive results while ligands bearing cyclohexyl groups gave

none of the desired product. A range of aryl chlorides were successfully coupled including activated electron-poor aryl chlorides and heteroaryl chlorides as well as de-activated electron-rich aryl chlorides.



Scheme 1.13 Diaryl ether synthesis from aryl chlorides

Thus far, a number of structurally diverse ligands have been employed to effect *C-O* bond formation. Recently, a report by Buchwald *et al.* outlined the use of tunable ligands that allow intermolecular palladium catalysed *C-O* bond formations.[80] The most effective of the ligands described are depicted in **Figure 1.5**. They claim the key to their success is the ability to match the size of the ligand to that of the combination of the substrates.

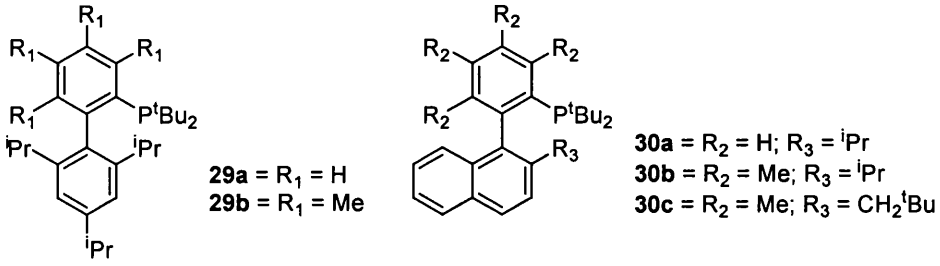


Figure 1.5 New series of 'tunable' ligands from the group of Buchwald

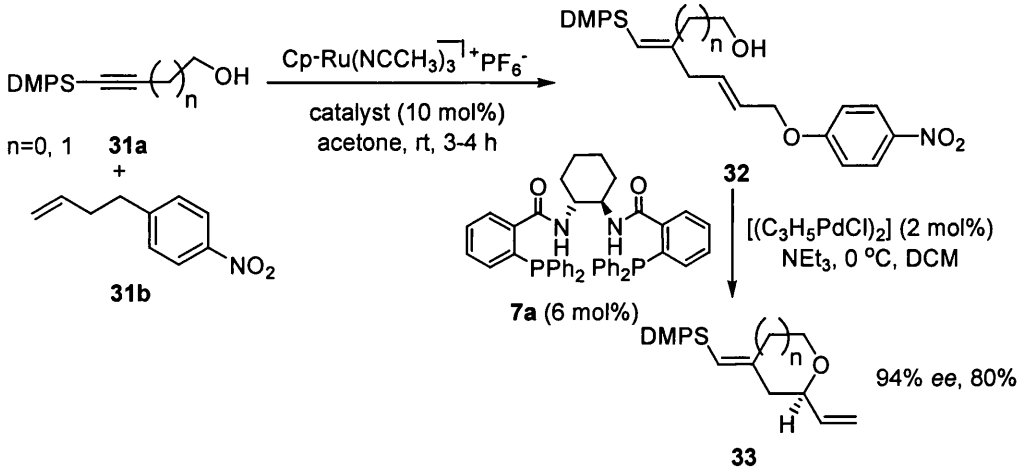
In general, the ligands **30b** and **30c** were suitable for the largest proportion of the reactions carried out including cross-coupling reactions between secondary alcohols with deactivated aryl halides, with almost complete suppression of the β-hydride elimination side reaction when carried out in Bu_3N as solvent. Ligands **29b**, **30a** and **30b** were found to be more effective for the cross coupling of primary alcohols with aryl bromides.

Individual palladium catalysed *C-O* bond formations include the synthesis of *meso*-aryloxy- and alkyloxy-substituted porphyrins from the cross coupling of *meso*-bromoporphyrins and an alcohol[81] and also the asymmetric annulation of benzene-1,2-diol with racemic, unsymmetrical secondary propargylic carbonates to give mixed diether products.[82]

1.7 Palladium Catalysed Intramolecular *C-O* Bond Formations

The following section briefly reviews some of the main advances in intramolecular *C-O* bond formation methodology which also incorporate tandem or sequential reaction sequences involving both inter- and intramolecular transition metal catalysed *C-C*/*C-O* cross-coupling reactions. A tandem reaction is defined as a reaction in which the preliminary step generates a functional group that is involved in the subsequent reaction. There have been many examples to date involving *C-C* couplings employing Heck,[83,84] Stille,[85,86] Sonogashira[87] and Suzuki reaction conditions[88] but fewer mixed *C-X* systems. Methodology towards the preparation of the benzofuran substructure will be discussed in more detail in **Chapter 3**.

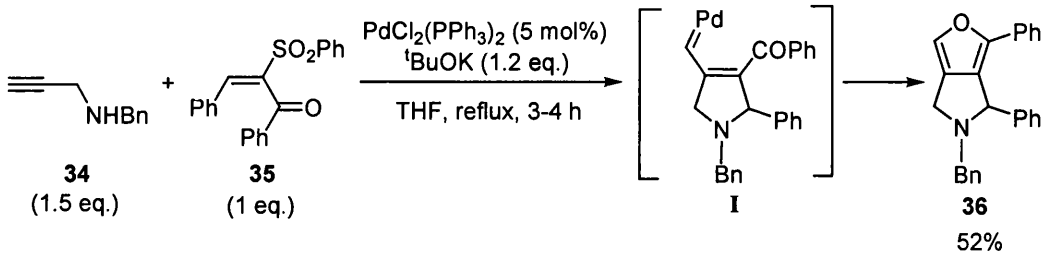
A palladium catalysed asymmetric allylic alkylation reaction **32-33** has been combined with a ruthenium catalysed ene-yne coupling **31-32** under stereocontrol to give the desired oxygen heterocycle as a single regio- and geometric isomer in a one-pot synthesis (**Scheme 1.14**).[89,90] It is essential for the two catalyst systems to complement each other and not to distort the 'chiral pocket' that is crucial for enantioselectivity. It was observed that the nucleophilic addition step in the catalytic cycle was the enantiodiscriminating step, the level of control exercised by the ligands increasing for the oxygen heterocycles. The yield of the overall process was also much higher than the combined individual yields of the isolated products.



Scheme 1.14 One-pot enantio- and diastereoselective synthesis of heterocycles

Several groups have independently reported the synthesis of furan and pyrrole derivatives by palladium catalysis in one step and one-pot. Furo[3,4-*c*]-fused heterocycles **36** have been efficiently prepared from propargylic amines or alcohols with varying sub-structures **34** and sulfone-based, activated alkenes **35** (**Scheme 1.15**).[91]

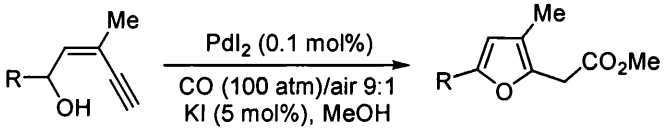
The mechanism has been rationalised by new methodology based on a Michael-addition-carbocyclisation: an alkenone carbene **I** is generated by applying a tandem Michael-addition-carbocyclisation to an arylidene *β*-ketosulfone **35**, subsequent internal trapping of the electrophilic carbene by the carbonyl oxygen produces a variety of furans **36**.



34 (1.5 eq.) + **35** (1 eq.) → **I** → **36** 52%

Scheme 1.15 One-step synthesis of furo[3,4-*c*] heterocycles

Methyl furan-2-acetates **38** can be formed by palladium catalysed cyclisation and carbonylation of 5-hydroxyenynes **37** (**Scheme 1.16**).[92] Both a high carbon monoxide partial pressure and an excess of KI proved necessary in order to direct the catalytic process toward the carbonylative pathway, preventing protonation of the vinylpalladium intermediate. A competitive cycloisomerisation side reaction in which dimethylfurans are formed was also observed.



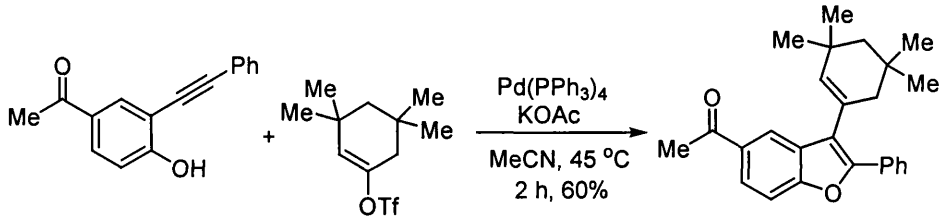
37 → **38** 55-82%

Scheme 1.16 Palladium-catalysed oxidative cyclisation-alkoxycarbonylation of (*Z*)-2-en-4-ynols

Tri- and tetra-substituted furans and pyrroles have also been synthesised by a heterobimetallic catalyst system comprising of a thiolate-bridged ruthenium complex [Cp*RuCl(μ-SMe)$_2$RuCp*Cl] and $PtCl_2$.[93] The unrelated catalysts promote different steps in the reaction sequence. This method is not as cost effective as a cheaper, one metal source catalyst system employing palladium.

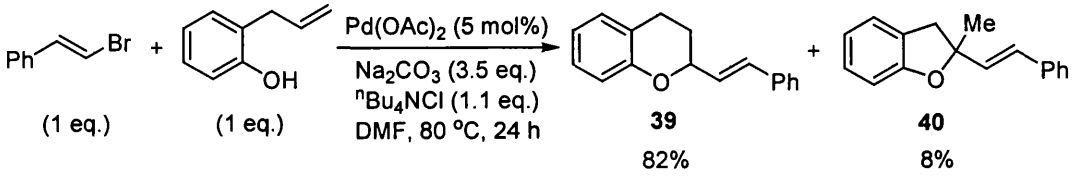
Poly-substituted benzofurans have been prepared from *O*-alkynylphenols and vinyl triflates under traditional catalytic conditions, $Pd(PPh_3)_4$/KOAc in acetonitrile at 45 °C (**Scheme 1.17**). Palladium catalysed substitution reactions can be effective in producing substituted heterocycles at *C-X*/*C-OTf* activated sites on the ring systems.[94] A PdI_2-

thiourea and CBr_4 co-catalyst system has also been developed for carbonylative cyclisation of both electron-rich and electron-deficient *O*-hydroxylarylacetylenes to the correnspondingly 2,3-disubstituted benzo[*β*]furans.[95]



Scheme 1.17 Poly-substituted benzofuran synthesis

In 1998, Larock described the synthesis of cyclic aryl ethers *via* the palladium-catalysed cross-coupling of unsaturated phenols and vinyl halides or triflates (**Scheme 1.18**).[96] Substituted dihydrobenzopyrans **39** and dihydrobenzofurans **40** were synthesised in moderate to excellent yields *via* a proposed mechanism involving an initial vinylpalladium addition to the alkene (Heck reaction), rearrangement of the π-allylpalladium intermediate with subsequent intramolecular nucleophilic displacement of the palladium by the phenol.

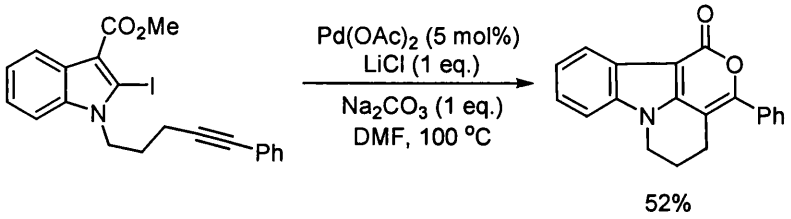


Scheme 1.18 Cross-coupling of unsaturated phenols and vinyl halides

The palladium catalysed coupling of terminal alkynes with *o*-iodophenols, with subsequent cyclisation to afford benzofuran derivatives, often occurs in one-pot. A review by Larock in 1999 described the palladium catalysed cross coupling reactions between a number of different dienes with *o*-halophenols to give the corresponding cyclic products.[64] Palladium catalysed cyclisation of substituted *o*-iodophenols will be discussed in more detail in **Chapter 3**.[64,97]

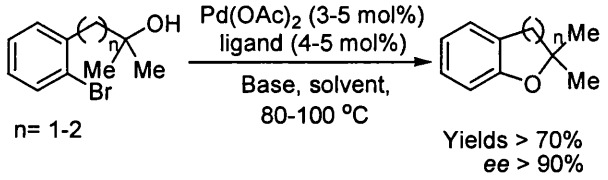
A number of reactions employing alternative oxygen nucleophiles have been reported including a range of enolates, carboxylates and siloxanes, some of which will be covered in more detail in **Chapters 3** and **4**. For example, a number of *N*-substituted 2-bromo/iodo-indole-3-carboxaldehydes bearing a tether with a *C-C* triple bond have been prepared, and an intramolecular palladium catalysed annulation successfully optimised to give a number of γ-carboline derivatives in good yields.[98] The palladium-catalysed

annulation of an analogous substituted carboxylate derivative involves a new *C-O* bond formation to form a cyclic ester (**Scheme 1.19**).



Scheme 1.19 Cyclisation of nucleophilic carboxylate moiety onto an alkenyl group

Scheme 1.20 depicts the general reaction for the intramolecular formation of aryl ethers proposed and effected by Buchwald *et al.*[99-101] The reactions with tertiary alcohol substrates were successful in the presence of Tol-BINAP, BINAP or dppf **12c** ligands at >80 °C in toluene with either $Pd_2(dba)_3$ or $Pd(OAc)_2$ and either NaO^tBu or K_2CO_3 as base.[100] The catalytic system employed was found to be compatible with a number of functional groups including acetals, silyl ethers and amides. In addition, five-, six- and seven-membered heterocycles were synthesised in good yields from primary, secondary and tertiary alcohols.



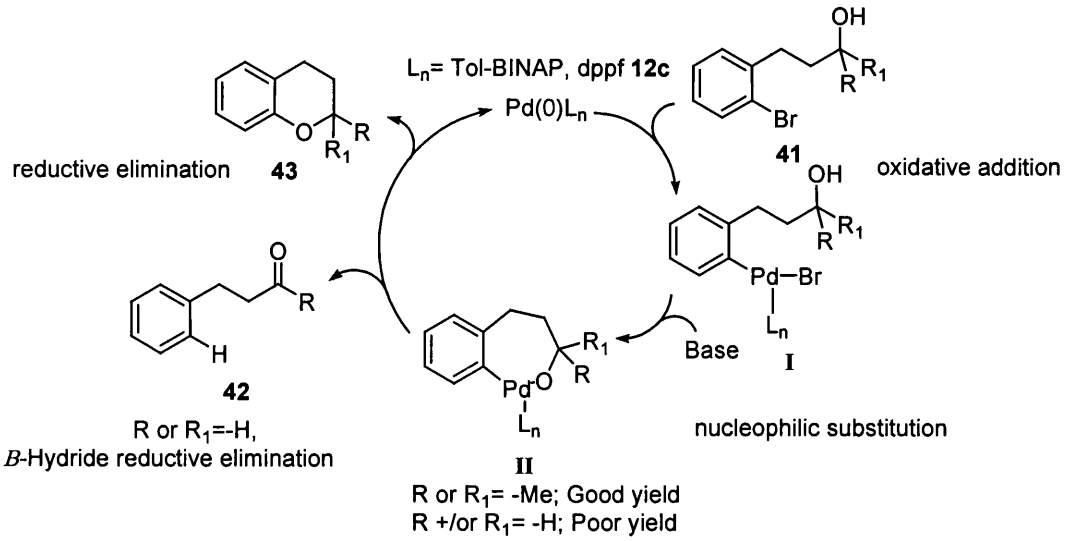
Conditions: Ligand: Tol-BINAP, dppf **12c**; Base: K_2CO_3, NaO^tBu, Solvent: toluene, 1,4-dioxane[7]

Scheme 1.20 Palladium catalysed synthesis of cyclic aryl ethers

Primary and secondary alcohols under these conditions gave only the debrominated product due to a *β*-hydride elimination side reaction to form the ketone (**Scheme 1.7**). It has since been proven that primary and secondary alcohols intramolecularly couple in the presence of a di-*tert*-butylphosphinobinaphthyl ligand **3b**.[99] The reaction conditions responsible for the analogous palladium-catalysed amination reaction are ineffective for *C-O* bond formations ($Pd_2(dba)_3$, dicyclohexylphosphinobiphenyl ligand **3a**, NaO^tBu).

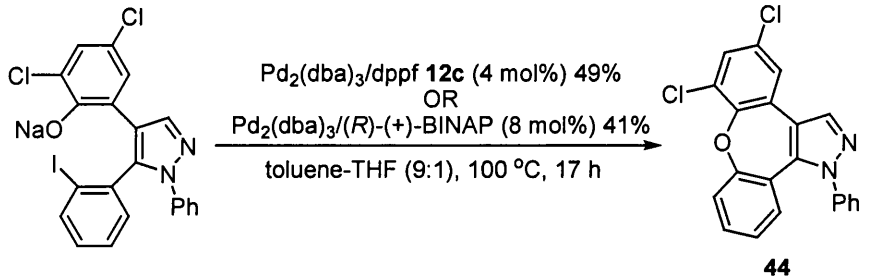
Scheme 1.21 depicts the catalytic cycle for an intramolecular *ipso*-substitution of an aryl halide with an alcohol. The main catalytic steps remain the same as for the analogous intermolecular reaction. The palladium oxidatively adds into the aryl-bromide bond to give intermediate **I**. The alcohol substituent is subsequently deprotonated and the alkoxide nucleophilically substitutes the bromide counterion to give a new oxapalladacycle intermediate **II**. This intermediate can either undergo *β*-

hydride elimination to give a ketone **42** or reductive elimination to give the desired cyclic product **43**.



Scheme 1.21 General catalytic cycle for the formation of cyclic aryl ethers

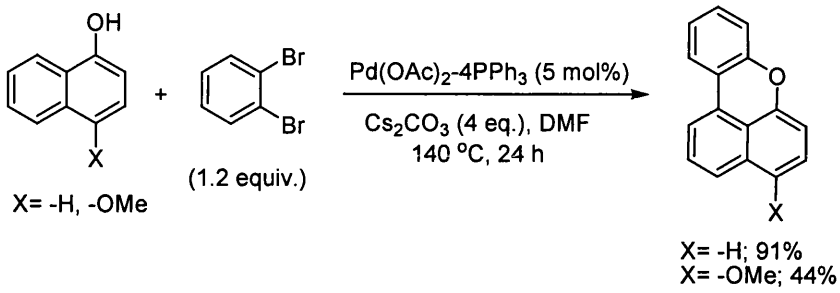
Intramolecular diaryl ether formation has been reported in the literature *via* the usual cross coupling of an aryl halide functional group and a proximate phenol functional group (*cf.* analogous intermolecular reaction, section **1.6**). Dominguez *et al.* described the preparation of dibenzoxepino[4,5-*d*]pyrazoles **44** employing the coupling reaction of phenoxides with aryl iodides and non-activated aryl moieties (**Scheme 1.22**). They found that, in general, the catalyst generated from $Pd_2(dba)_3$ and dppf **12c** as ligand was the better system although employing BINAP as ligand also proved useful. This may be a consequence of their similar bite angle values[102] and thus their comparable ability to promote reductive elimination. When traditional catalytic conditions were employed, only dehalogenated product was observed.



Scheme 1.22 Cyclic diaryl ethers synthesis

An alternative preparation of cyclic diaryl ethers has also been successful employing successive *C-C*/*C-O* bond forming reactions involving simple arylations of 1,2-diiodo-

and 1,2-dibromobenzenes (**Scheme 1.23**).[103] Intermolecular diaryl *C-C* bond formation precedes intramolecular diaryl ether *C-O* bond formation. Unfortunately for the reaction to proceed, it must be carried out at elevated temperatures >140 °C which restricts its utility.



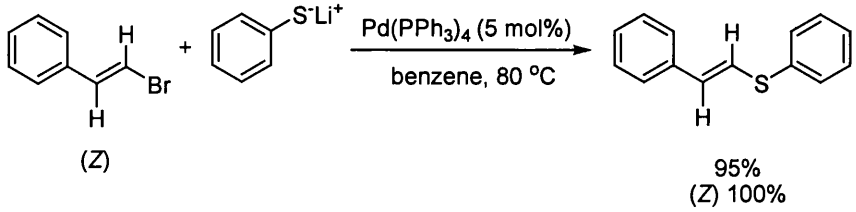
Scheme 1.23 Cyclic diaryl ethers from phenols and aryl halides

1.8 Palladium Catalysed *C-S* Bond Formations

There are far fewer examples of palladium catalysed *C-S* bond forming reactions in the literature than *C-O* bond forming reactions. Sulfur possesses distinctive properties compared to oxygen: lower electronegativity, increased nucleophilicity, higher polarisability and, in particular, its comparable ease of oxidation. All of these characteristics contribute to the potential for the sulfur moiety to poison the palladium by means of an irreversible covalent interaction between the two 'soft' centres. There have been many instances reported of halogen displacement of activated or non-activated aryl halides by a sulfenyl nucleophile simply by heating in polar, aprotic solvents without the need for catalysis.[104,105] Undesirably, elevated temperatures (>140 °C), photoinitiation techniques[106] or the use of specific solvents such as DMSO or NMP are required. Methods that can avoid such measures have been sought[107] including both copper[108,109] and nickel catalysed variations.[110] Descriptive examples are given herein to emphasise the principal reactions undertaken for the preparation of thioethers employing palladium catalysis.

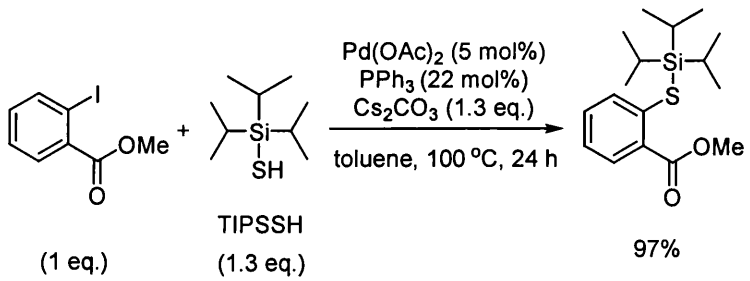
Murahashi *et al.* described one of the first palladium-catalysed sulfenylation reactions of alkenyl halides.[111] They were interested in the synthetic utility of the prepared vinyl sulfides as equivalents of carbonyl compounds[112,113] and terminal acetylenes.[114] Application of the general palladium catalyst, $Pd(PPh_3)_4$, to a mixture of (*Z*) or (*E*)-*β*-bromostyrene and lithium benzenethiolate in benzene at 80 °C afforded isomerically pure vinyl sulfides (**Scheme 1.24**). They also reported that the reaction did not take

place in the absence of the Pd catalyst and only occurred upon alternative treatment with copper methanethiolate at elevated temperatures of 200 °C.



Scheme 1.24 Sulfenylation of *β*-bromostyrene

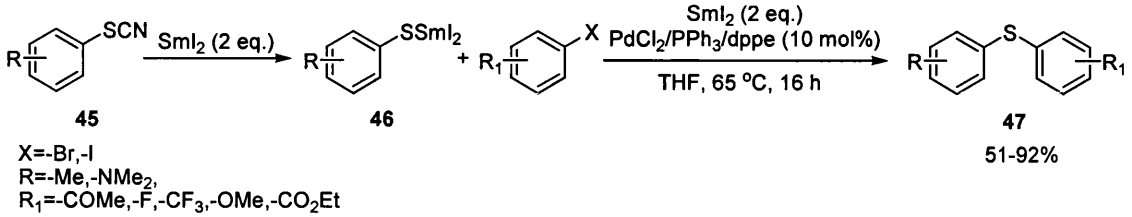
Several reports have described palladium-catalysed cross-coupling reactions of protected thiol as sulfur donors.[115] Successful studies have employed activated stannylthiolates as the sulfenylation reagent coupling with vinyl bromides[116] and aryl halides[117] in the presence of the seemingly robust palladium catalyst, $Pd(PPh_3)_4$, in a Stille type cross-coupling reaction. Due to the preferred avoidance of toxic tin reagents, alternative ways of activating the thiol group towards *C-S* bond formation have been investigated. Arnould *et al.*[118] and later Brase and Kreis[119] reported the formation of aryl silyl sulfides from aryl triflates and NaSTIPS or aryl halides/triflates and TIPSSH with Cs_2CO_3 respectively (**Scheme 1.25**). Both employed catalyst systems with PPh_3 as the ligand, either by *in-situ* generation from $Pd(OAc)_2$ and PPh_3 or by direct use of the, more expensive, pre-formed catalyst $Pd(PPh_3)_4$. Selective removal of the TIPS group with TBAF gave the analogous thiol substrates in moderate to excellent yields.[118] Certain substrates also proved labile to purification by silica, giving rise to the thiol analogues.[119]



Scheme 1.25 Aryl silyl sulfide synthesis employing palladium catalysis

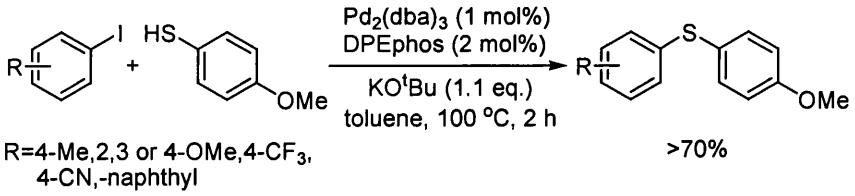
Still and Toste reported a novel use of samarium diiodide as a reductant of aryl thiocyanates **45** to give an aryl samarium thiolate **46** which can readily undergo palladium catalysed cross-coupling to give mixed aryl sulfides **47** in the presence of a Pd(II) catalyst (**Scheme 1.26**).[120] It was proposed that the Pd(II) catalyst is reduced *in-situ* to Pd(0) by a second equivalent of samarium diiodide. The catalytic cycle can then proceed in the usual fashion: oxidative addition to the arylhalide, *pseudo-*

transmetallation of the samarium thiolate to the intermediate palladium complex followed by reductive elimination to give the newly formed mixed aryl sulfide product **47**. An unusual, mixed ligand, catalyst system generated from $PdCl_2/PPh_3$ and dppe was found to be optimal, as reported previously by Baranano and Hartwig.[121] For reasons unknown, the application of a catalyst system employing dppe as ligand was found to improve the yields for reactions involving thiol nucleophiles, alleviating issues of palladium poisoning by the thiolate.



Scheme 1.26 Formation of mixed aryl sulfides from thiocyanates

It was not until 2001 that a more general catalyst system for the preparation of both electron-rich and electron-poor mixed biaryl thioethers was reported by Schopfer and Schlapbach (**Scheme 1.27**).[122] They described an efficient palladium catalysed coupling between aryl iodides and aryl thiols in the presence of a catalyst generated from $Pd_2(dba)_3$ and the bidentate phosphine based ligand, DPEphos, using KO^tBu as base to give a range of thioethers in excellent yields.

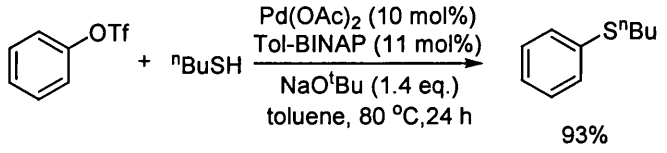


Scheme 1.27 Palladium(0) catalyst for the synthesis of mixed aryl sulfides

Several groups reported the development and expansion of this novel reaction to encompass alternative combinations of coupling partners. Itoh and Mase found that simple substitution of the ligand DPEphos for Xantphos in the presence of $^iPr_2EtN$ as a base in 1,4-dioxane at elevated temperatures allowed for the efficient coupling of aryl bromides, aryl triflates and activated aryl chlorides with a variety of substituted aryl and alkyl thiols as the sulfide equivalents.[123] They found that the choice of base was critical to the reaction progress. Inorganic bases such as Na_2CO_3, K_3PO_4, KF or CsF or stronger bases such as NaO^tBu or KO^tBu decreased the yields. An investigation by Perrio *et al.* substantiated these results utilising alternative substituents on the same general coupling

partners employing a catalyst generated from $Pd_2(dba)_3$ and Xantphos although this time in the presence of K_2CO_3 as the base in xylene at 140 °C.[124]

Zheng *et al.* established a palladium system capable of catalysing the cross-coupling between aryl triflates and sodium alkanethiolates to give mixed aryl alkyl sulfides (**Scheme 1.28**).[125] The catalyst combination: $Pd(OAc)_2$, BINAP with LiCl as a halide additive, gave excellent yields of the coupled product. However, a more simplified catalyst partnership between $Pd(OAc)_2$ and Tol-BINAP gave comparable results and was, therefore, the catalyst of choice. Employment of the bulky, bidentate binaphthyl ligands seems to underpin the success of this catalyst system. Although good conversions were achieved with electron-poor and electron-neutral aryl triflates, the reaction did not tolerate electron-rich aryl triflates or other thiol nucleophiles such as PhSH or KSAc.

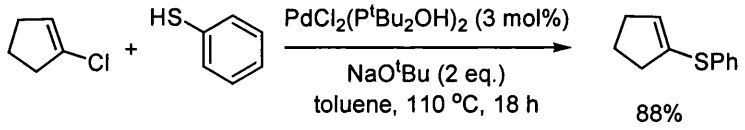


Scheme 1.28 Palladium-catalysed formation of aryl-alkyl sulfides

Buchwald also reported a general and efficient catalyst system for the cross-coupling of aryl halides with alkyl and aryl sulfides generated from $Pd(OAc)_2$ (2 mol%) and the ligand 1,1'-*bis*(di*iso*propyl-phosphino)ferrocene **12a** (2.4 mol%) with NaO^tBu as base.[126] In the same year, the group of Zhang described the synthesis of a new family of *meso*-arylsulfanyl and alkylsulfanyl-substituted porphyrins employing a direct palladium-mediated *C-S* bond formation between *meso*-brominated porphyrins and thiols.[127] A comprehensive ligand screen showed that a number of structurally different *bis*-chelating and mono-phosphine ligands as well as an *N*-heterocyclic carbene ligand could execute the model coupling of 4-methoxythiophenol with a prepared *meso*-brominated porphyrin. However, both DPEphos and BINAP were found to be the ligands of choice for a wide range of substituted thiol substrates including 2-naphthalenethiol, benzothiazole-2-thiol, *bis*-thiols and *ortho*-substituted arylthiols.

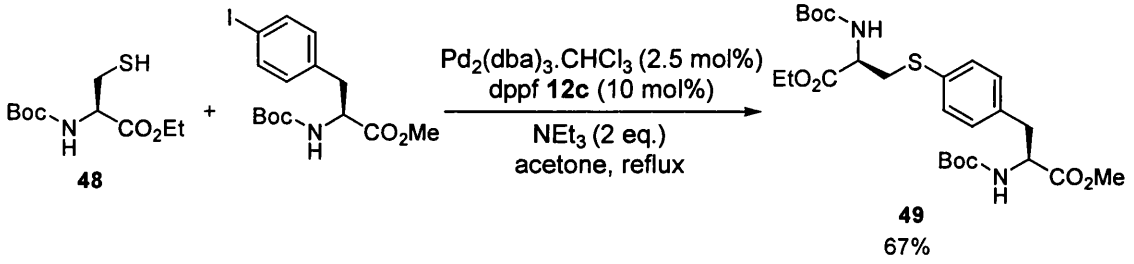
A succeeding report by Li highlighted only one further example of a palladium catalysed cross-coupling reaction between *tert*-butylthiol and an aryl bromide in the presence of a preformed, air stable palladium-phosphine oxide complex.[128] They later expanded this work to include the air-stable palladium catalysed *C-S* bond formations of

vinyl chlorides to give the corresponding thioethers in respectable yields (**Scheme 1.29**).[129]



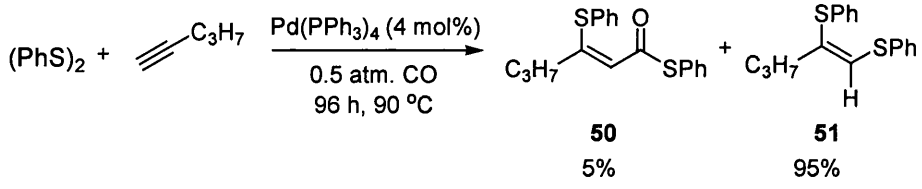
Scheme 1.29 Palladium-catalysed formation of vinyl-aryl sulfides

In 2003, the group of Campagne reported the effective palladium catalysed cross-coupling reaction of cysteine thiols **48** with aryl and vinyl halides to give cysteine thioethers **49** (**Scheme 1.30**).[130,131] They found that a catalyst generated from $Pd_2(dba)_3.CHCl_3$ and dppf **12c** was best in the presence of triethylamine as base. A simple test reaction to determine the role of the base showed that it could be replaced by an HX-scavenger such as propylene oxide, although products were recovered in slightly lower yields suggesting that the base was acting as both a base and HX-scavenger.



Scheme 1.30 Palladium-catalysed cross-coupling of a cystein derivative with an aryl iodide

A more unusual study carried out by Knapton and Meyer towards a four-component palladium-catalysed cross-coupling to yield (*Z*)-*β*-selenylacrylamides lead to the attempted carbonylative addition of diphenyl disulfide to 1-pentyne (**Scheme 1.31**).[132] In the presence of the catalyst $Pd(PPh_3)_4$ only trace amounts of the carbonylative addition product **50** were recovered with almost quantitative yield of the simple addition product **51**.



Scheme 1.31 Palladium-catalysed alkyne-sulfide cross-coupling

Our contribution to both palladium-catalysed *C-O* and *C-S* bond formations will be outlined in the following section.

1.9 References

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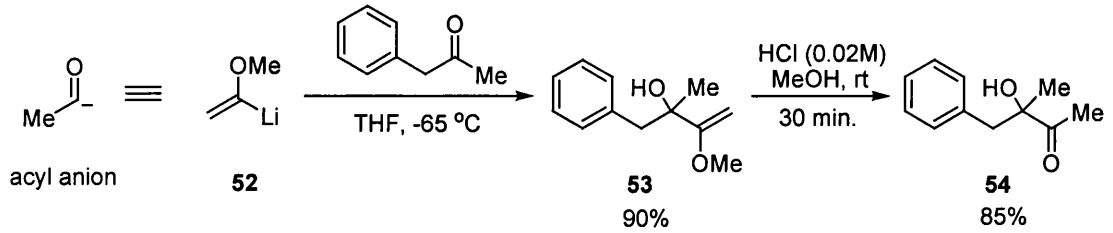
Chapter 2 Application of Palladium Catalysed *C-O* Bond Formations to the Synthesis of Enol Ethers

To begin our investigation towards a novel intermolecular palladium catalysed *C-O* bond formation with a view to desymmetrise *bis*-vinyl triflate substrates we first had to establish palladium catalytic conditions for a simpler mono-vinyl triflate analogue. To the best of our knowledge, the intermolecular palladium catalysed cross-coupling reaction between a vinyl triflate and a substituted phenol had yet to be reported and in light of this we successfully synthesised a range of enol ethers. Our approach is detailed herein.[1]

2.1 Enol Ethers

2.1.1 Representative applications in synthesis

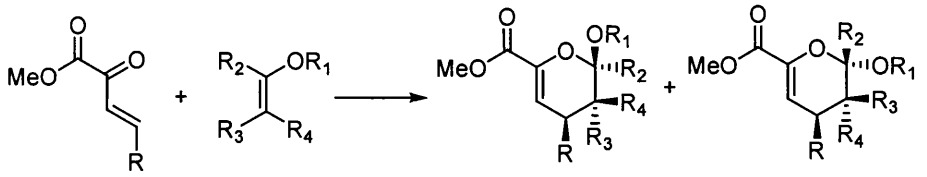
Enol ethers are important functional groups and building blocks for use in organic synthesis. They are also used on an industrial scale as monomers in the production of oxygen containing vinyl polymers.[2] In 1974, Baldwin *et al.* reported that metalated enol ethers are versatile and efficient practical reagents for nucleophilic acylations (**Scheme 2.1**).[3] The metalated species **52** can be synthesised by lithiation of the corresponding methyl vinyl ether with *tert*-butyllithium in THF at –65 °C. The lithiated intermediate can subsequently be trapped by a number of electrophiles *eg.* aldehydes, ketones and alkyl, acyl or allyl bromides to give substituted enol ethers **53**. These can be further elaborated, *eg.* cyclopropanation of the alkene portion[4] or converted to their analogous ketones **54** by mild hydrolysis.



Scheme 2.1 α-Methoxyvinyllithium as a nucleophilic acyl anion equivalent

Enol ethers are also useful as dienophile substrates in accelerated inverse electron demand Diels-Alder reactions.[5] **Scheme 2.2** illustrates the general [4 + 2] cycloaddition reaction between an electron-deficient diene **55** and an electron-rich enol ether

dienophile **56**. This reaction has been executed successfully under thermal, pressure-promoted and Lewis acid catalysed conditions. Both *endo* **57a** and *exo* **57b** geometries can be attained with the *endo* geometry predominating (*cf.* traditional Diels-Alder).



55 R= -OMe, -Ph

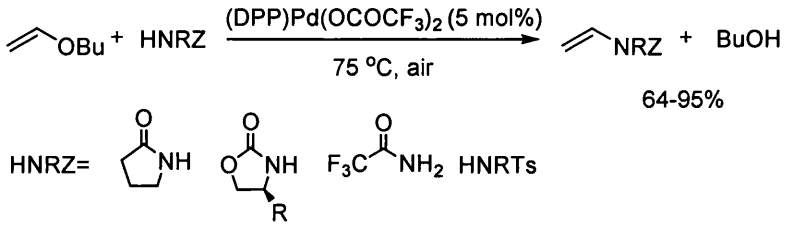
56 R_1=-Me, -Et, -Bn; R_2=-H, -OMe; R_3=-H; R_4=-H, -Me, -OMe, -COMe, $-COCO_2Me$

57a *endo*

57b *exo*

Scheme 2.2 Enol ether adducts as Diels-Alder dienophiles

More recently Stahl *et al.* described a palladium-catalysed vinyl transfer reaction from vinyl ethers to nitrogen nucleophiles which proceeded in good yields with a phenanthroline-based catalyst in air (**Scheme 2.3**).[6,7] They opted for a Pd(II) catalyst as Pd(0) catalysts are generally incompatible with an aerobic atmosphere and are not expected to undergo efficient oxidative addition to vinyl ethers. The air stable Pd(II) catalyst (DPP)Pd(TFA)$_2$ was found to be effective with a number of amide and tosylamide nucleophiles. Unfortunately, saturated primary and secondary amines were not well tolerated.

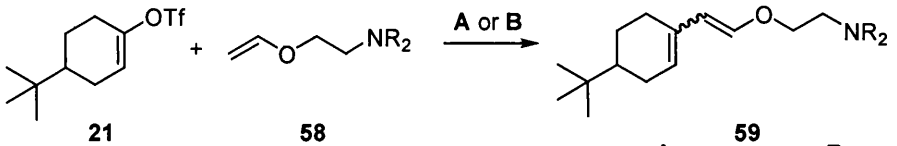


Scheme 2.3 Synthesis of enamides *via* transfer vinylation

Although mercuric salts are known to promote vinyl transfer to oxygen nucleophiles,[8,9] when Stahl applied them to the equivalent nitrogen reaction they proved less effective. The established Pd(II)phenanthroline catalytic conditions are similar to those previously identified for vinyl transfer to oxygen nucleophiles for the preparation of enol ethers.[4,10,11]

Stadler and Larhed *et al.* report a novel terminal chelation-controlled Heck vinylation of electron-rich amino-functionalised vinyl ethers **58** with vinyl triflates, displaying high regioselectivity to give the corresponding 1-alkoxy-1,3-butadienes **59** in moderate to

good yields (**Scheme 2.4**).[12] Typically, vinylation of an electron-rich alkene under catalytic conditions affords the α-branched 1,3-butadiene product and this internal chelation-controlled approach is the first to afford linear 1,3-butadiene products.



R=Me: 56% *E*/*Z*=94:6; 74% *E*/*Z*=89:11
R=Et: 73% *E*/*Z*=86:14;70% *E*/*Z*=89:11

Conditions: vinyl triflate (0.5 eq.), vinyl ether (0.75 eq.), DMSO (1.5 mL), 60 °C, 24 h; **A**: $Pd_2(dba)_3.CHCl_3$ (3 mol%), $HP^tBu_3BF_4$ (10 mol%); **B**: $Pd(OAc)_2$ (1 mol%), PPh_3 (3 mol%).

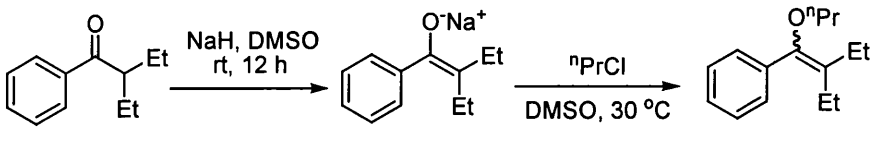
Scheme 2.4 Synthesis of linear, electron-rich 1,3-butadienes

The initial chelation of the amino group to the palladium centre directs the chelation of the vinyl functionality with subsequent insertion of the palladium into the π-system. This insertion is controlled by the chelated ring size and is followed by collapse of the palladacycle *via* a *syn*-β-elimination to give the terminal product. The resulting 1,3-butadienes were shown to react effectively as the diene component in a microwave-assisted Diels-Alder reaction employing dimethyl acetylenedicarboxylate (DMAD) as the electron-poor dienophile partner.

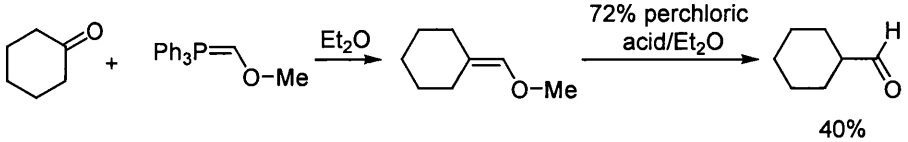
2.1.2 Synthesis of Enol Ethers

Non-metal mediated syntheses

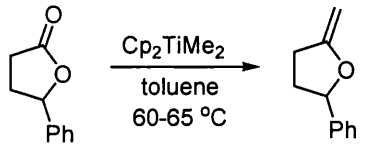
Traditional methods for the preparation of enol ethers include *O*-alkylation of enolates (**equation I**),[13] Wittig alkenylation employing *O*-substituted phosphoranes (**equation II**),[14] titanium mediated alkenylation of carboxylic esters (**equation III**),[15] base catalysed addition of alcohols to acetylenes,[16] substitution of silyl enol ethers[17] and dehydrohalogenation of 2-haloethyl ethers (**Scheme 2.5**).[18]



88% [I]



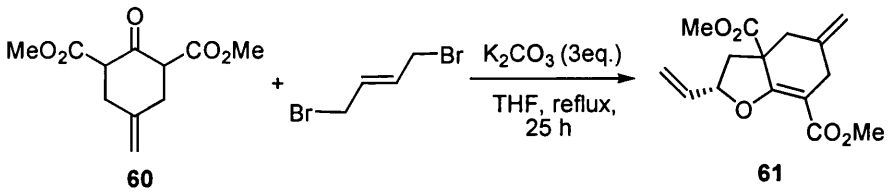
40% [II]



41% **[III]**

Scheme 2.5 Traditional enol ether syntheses

Cyclic enol ethers **61** have been synthesised from α,α'-diactivated ketones **60** with *trans*-1,4-dibromo-2-butene *via* a stereoselective tandem *C*- and *O*-cycloalkylation in the presence of base (**Scheme 2.6**).[19,20,21] The cyclic enol ethers can then undergo simple hydrolysis to afford hemi-acetals or γ-hydroxy ketones with resulting stereocontrol of remote sterogenic centers.[19] It is imperative that the alkene geometry is *trans* as the corresponding *cis*-alkenes undergo a *C-C* dialkylation to give a bicyclic ketone derivative.[20] Cyclopentanone, cyclohexanone and cycloheptanone polycyclic enol ethers have been successfully synthesised. The mild reaction conditions allow for a range of functionality to be tolerated.



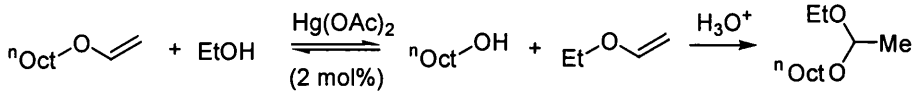
60 **61**
93%

Scheme 2.6 Preparation of cyclic enol ethers

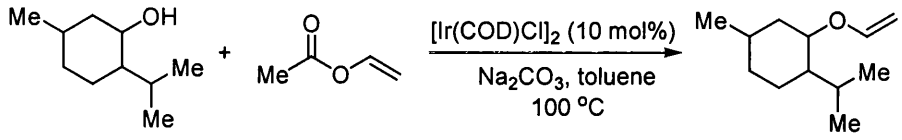
Metal-mediated syntheses

The synthesis of aryl enol ethers is particularly challenging and the methods for their preparation are more limited, with transvinylation procedures being, in general, the most useful (**equation IV/ V, Scheme 2.7**).[22,23] Transvinylation is a term given to the reaction in which a vinylic function bonded to an oxygen in an ester or ether is transferred to another oxygen atom in a second ester or ether. In the 1950s, mercuric salts of weak carboxylic acids were reported to be particularly effective in catalysing the transfer of vinyl groups from vinyl ethers to alcohols to give the substituted vinyl ether (**equation IV**).[22] A second vinyl transfer can proceed in the presence of acid to give the corresponding acetal. The reaction is thought to be reversible due to symmetrical intermediates, with the equilibrium being disturbed by flash-stripping the volatile products from the catalyst or by deactivating the catalyst.

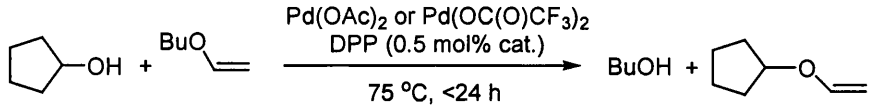
Recent studies have discovered that the reaction can be catalysed by less toxic metal catalysts *eg.* iridium[23] and palladium.[24] The iridium-catalysed reaction relies upon the use of vinyl acetate as the sole vinyl donor, to give terminal aryl/alkyl vinyl ethers, with no acetal side product observed (**equation V**). Analogous rhodium, ruthenium and platinum complexes were inert under these optimised conditions.



[IV]



[V]



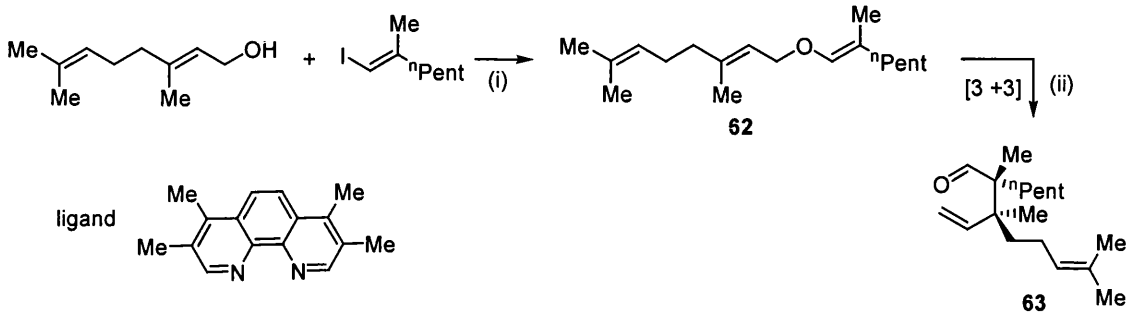
[VI]

Scheme 2.7 Transvinylation methods

A palladium catalyst generated from $Pd(OAc)_2$ and either a bidentate 2,2'-bipyridyl or 1,10-phenanthroline ligand has been successfully employed in transfer vinylations of; protected sugars,[25] steroids,[4] primary, secondary and tertiary alcohols and a selection of primary and secondary allyl vinyl ethers.[24] **Equation VI** depicts a representative palladium-catalysed transfer vinylation between a secondary alcohol and a simple alkyl vinyl ether. It was found that the efficiency of the reaction was greatly improved by interchanging the palladium source counterion from acetate to trifluoroacetate. This is a direct result of the weaker coordinating ability of the trifluoroacetate ion, resulting in an increased rate of reaction. Such methods are limited to simple ethenyl ethers as steric bulk around the α-carbon prohibits the formation of the oxy-palladate or the η^2-vinyl alkoxide intermediates.

In 1992, Keegstra *et al.* described the first example of a copper catalysed alkyl enol ether synthesis *via* cross-coupling of vinyl bromides with sodium methoxide as the sole alkoxide source employed.[26] Buchwald *et al.* described another simple method for the synthesis of allyl vinyl ethers **62** involving the stereospecific coupling of an allylic alcohol and a vinyl halide, applying a copper based catalyst (**Scheme 2.8**).[27] Vinyl iodides were shown to be more compatible with the conditions in comparison to vinyl bromides and the rate of reaction varied significantly with type of alcohol, generally in

the order aliphatic > allylic ≅ propargylic > benzylic. Complete retention of configuration of the double bond geometry in the vinyl ether product indicated that a catalytic cross-coupling process and not a nucleophilic substitution was in operation. A subsequent Claisen rearrangement process **62-63** could be brought about by increasing the temperature and the equivalents of base and carrying out the reaction under an inert atmosphere. Both steps were high yielding with high diastereoselectivity.

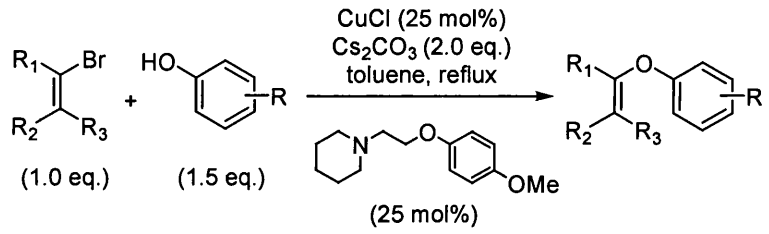


(i) CuI (10 mol%), ligand (20 mol%), Cs_2CO_3 (1.5 eq.), 80 °C, 12-48 h, toluene, air atm
(ii) CuI (10 mol%), ligand (20 mol%), Cs_2CO_3 (3 eq.), 120 °C, 48 h, *o*-xylene, Ar atm

77%
92:8 dr

Scheme 2.8 Domino copper catalysed *C-O* coupling/Claisen rearrangement process

Later in 2003, Wan *et al.* described a vinyl aryl ether synthesis by copper chloride catalysed coupling of vinyl bromides or iodides and substituted alcohols, phenols or thiols. The conditions used were based on the already established Ullmann diaryl ether reaction conditions.[28] Although they require significantly larger amounts of copper and ligand to execute the reactions, they do efficiently couple aryl substituted vinyl halides and terminal vinyl halides (**Scheme 2.9**).



Scheme 2.9 Copper-catalysed synthesis of aryl vinyl ethers

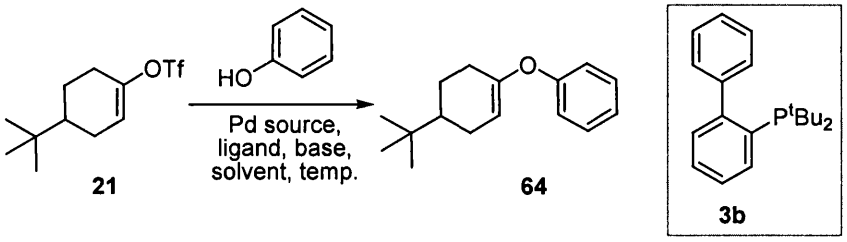
The approach that we have decided to investigate towards the preparation of a variety of substituted vinyl aryl ethers will use ketone enolates or their equivalents directly in the aryl ether formation step.

2.2 Intermolecular Aryl Enol Ether Synthesis from Vinyl Triflates

2.2.1 Optimisation of Catalyst Parameters

Variables: ligand, base and palladium source

To investigate the proposed synthesis we chose to use the corresponding vinyl triflate of 4-*tert*-butyl cyclohexanone **21**, as our initial coupling partner in combination with phenol. The preliminary coupling conditions investigated were based on those reported for aryl *C-O* systems and on those developed for alkenyl *C-N* bond formations. Recent investigations by Buchwald *et al.* have shown that palladium catalysts generated from electron rich biphenyl ligands have shown enhanced reactivity for *C-X* bond formations and thus, present an ideal system with which we began our investigations.[29,30]



21 **64** **3b**

Table 2.1 Catalyst:base optimsation

Entry	Palladium Source	Ligand	Base	Temp. (°C)	Time (h)	Conv. (%)	Yield (%)
1	$Pd(OAc)_2$	**3b**	NaO^{t}Bu	80	20	11	0
2	"	**3b**	K_3PO_4	80	24	0	0
3	"	**3b**	Cs_2CO_3	80	24	0	0
4	$Pd_2(dba)_3$	**3b**	NaO^{t}Bu	100	22	59	24
5	"	**3b**	K_3PO_4	100	25	45	-
6	"	**3b**	Cs_2CO_3	100	20	2	0
7[a]	"	**1b**	NaO^{t}Bu	100	18	45	30
8	"	**5a**	NaO^{t}Bu	100	24	0	0
9	"	**5b**	NaO^{t}Bu	100	24	0	0
10[b]	"	P(4-OMePh)$_3$	NaO^{t}Bu	100	20	50	40
11	"	P(^{t}Bu)$_3$	NaO^{t}Bu	100	18	51	<30
12[c,d]	"	(*rac*)-BINAP	NaO^{t}Bu	80	19	0	0
13	$Pd(OAc)_2$	(*rac*)-BINAP	Cs_2CO_3	80	22	0	0

Conditions: Pd source (2 mol% with respect to Pd), ligand (3 mol%), NaO^{t}Bu (1.4 eq.) or K_3PO_4/Cs_2CO_3 (2.0 eq.), phenol (1.2 eq.); **a**: work-up; filter through celite, eluting with hexanes followed by flash column chromatography (neutral alumina); **b**: impurities present; **c**: Pd source (3 mol%), ligand (9 mol%), NaO^{t}Bu (1.75 eq.), phenol (1.5 eq.); **d**: NaO^{t}Bu (2.3 eq.), phenol (2.0 eq.).

Employing a catalyst system generated from $Pd(OAc)_2$ and ligand **3b** in combination with NaO^tBu in toluene at 80 °C delivered 11% of the expected enol ether, while exchanging for the weaker bases K_3PO_4 or Cs_2CO_3 under the same conditions failed to produce any coupled product (entries 1-3, **Table 2.1**). An alternative palladium source $Pd_2(dba)_3$ proved the most effective; in combination with ligand **3b** and NaO^tBu it produced 59% conversion to the desired enol ether (entry 4). Again, employment of the weaker inorganic bases was less effective (entries 5 and 6). Evaluation of alternative electron-rich phosphine ligands **1b**, **5a**, **5b**, P(4-OMePh)$_3$, P(^{t}Bu)$_3$ and (*rac*)-BINAP, applying the $Pd_2(dba)_3$ and NaO^tBu system, delivered less successful catalyst systems in comparison to ligand **3b** (entries 7-12). The ligands were chosen for their differing electronic and steric properties; the bulkier, more electron rich mono-dentate ligands **1b**, P(4-OMePh)$_3$ and P(^{t}Bu)$_3$ commanded 50% conversions but did not rival ligand **3b** (entries 7, 10 and 11 respectively). Previously within the group, it had been shown that the catalyst generated from the combination of $Pd(OAc)_2$ and electron rich, bidentate ligand (*rac*)-BINAP was the most effective for the analogous *C-N* bond forming reaction to produce enamines, however, when applied to the present system no product was obtained (entry 13).[31]

Variables: stoichiometry and temperature

With the key combination of $Pd_2(dba)_3$, ligand **3b** and NaO^tBu, as the base, in hand, we next evaluated the effects of catalyst loading, equivalents of base and temperature.

All of the entries described so far employed 2 mol% palladium source and 3 mol% ligand (**Table 2.1**; entry 1, **Table 2.2**); increasing the ligand loading to 6 mol% gave only a slight improvement in conversion from 59% to 64% of the desired enol ether (entry 2), however, increasing both the palladium and ligand loading to 3 mol% and 9 mol% respectively, significantly improved the yield of enol ether to 74% (entry 9). Increasing the equivalents of phenol and base did not have a dramatic effect on the overall amount of product obtained (*cf.* entries 3 and 4; 7 and 8). Unfortunately, an elevation in temperature was mandatory as a mere 11% conversion was obtained at 50 °C (*cf.* entries 5-7 and 10). At elevated temperatures there was a notable influence of increasing the catalyst to ligand ratios, implying that both factors individually contribute to the progress of the reaction (*cf.* entries 2 and 9). Entries 10 and 11 show quantitatively the positive effect of opting for neutral work-up conditions in an attempt to deter the hydrolysis of the product during purification.

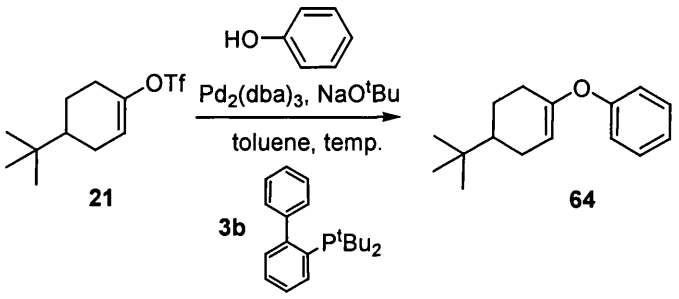


Table 2.2 Variable optimisation

Entry	Phenol (eq.)	$Pd_2(dba)_3$ (mol%)	ligand (mol%)	NaO^tBu (eq.)	Temp. (°C)	Time (h)	Conv. (%)	Yield (%)
1	1.2	2	3	1.4	100	22	59	24
2	1.2	2	6	1.4	100	19	64	48
3	1.5	2	6	1.75	100	5	-	28
4	2.0	2	6	2.3	100	5	-	29
5	1.5	2	6	1.75	50	22	11	0
6	1.5	2	6	1.75	80	22	22	13
7	1.5	3	9	1.75	80	22	40	26
8	2.0	3	9	2.3	80	22	48	33
9	1.2	3	9	1.4	100	19	74	31
10[a]	1.5	3	9	1.75	100	19	82	52
11[b]	1.5	3	9	1.75	100	20	95	85

Conditions: Reactions carried out on 0.6 mmol scale; **a**: work-up; filter through celite with diethyl ether followed by flash column chromatography (silica); **b**: work-up; filter through celite with hexanes followed by flash column chromatography (neutral alumina).

2.2.2 Scope of reaction

It was now necessary to explore the generality of our catalyst system with a selection of substituted phenols (**Table 2.3**). The 95% conversion obtained for the coupling of unsubstituted phenol translated to an 85% isolated yield of the enol ether (entry 1, **Table 2.3**).

Comparable conversions and yields were obtained for 4-methyl and 4-*tert*-butyl groups as well as the 3-*tert*-butyl group illustrating the effectiveness of the system when applied to bulky and neutral substituents (entries 2, 4 and 5). However, the process does not tolerate the presence of a 2-methyl group well (entry 3). Successful application to electron-rich phenols is shown with coupling of both 4- and 3-methoxy substituted phenols giving impressive conversions of 98% and 100% respectively (entries 6 and 7); poor isolated yields may be attributed to the increased instability of the products to hydrolysis upon purification. Again, the *o*-isomer of this substrate gave significantly

less product with only a 30% conversion (entry 8), presumably as a result of the increased steric hinderance around the active site.

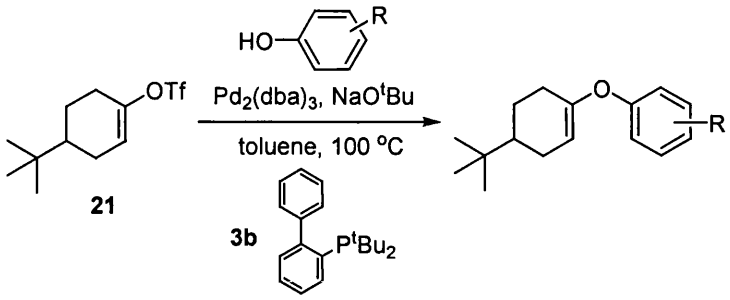
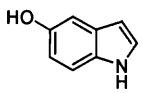
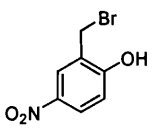


Table 2.3 Phenol scope

Entry[a]	Phenol		Time (h)	Conv.[b] (%)	Yield[c] (%)
1	Phenol	**64**	20	95	85
2	4-Me	**65**	23	100	80
3	2-Me	**66**	23	60	20
4	4-^{t}Bu	**67**	22	100	98
5	3-^{t}Bu	**68**	22	100	80
6	4-OMe	**69**	22	98	40
7	3-OMe	**70**	23	100	37
8	2-OMe		22	30	0
9	4-Ac	**71**	22	90	42
10	3-Ac	**72**	22	90	60
11	2-Ac		22	0	0
12	4-CN	**73**	20	-	45
13	3-CN	**74**	20	-	40
14	4-NO_2	**75**	22	95	60
15	4-Cl	**76**	23	75	50
16	2-F	**77**	23	95	70
17	3-NMe_2	**78**	23	90	45
18	3-NH_2		23	Mixtures of products	0
19			22	Mixtures of products	0
20			22	0	0

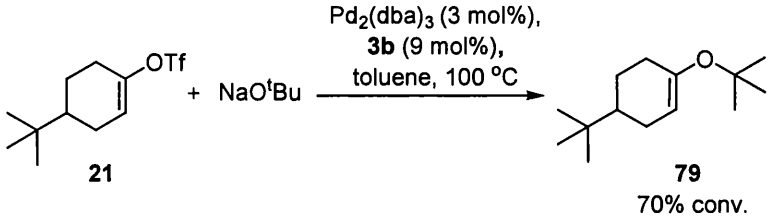
Conditions: a: Triflate (1.0 eq.), phenol (1.5 eq.), $Pd_2(dba)_3$ (3 mol%), ligand (9 mol%), NaO^tBu (1.75 eq.); **b**: measured by proton NMR; **c**: isolated yields of pure material.

Electron withdrawing substituents were also well tolerated. An acyl group was selected as a typical electron withdrawing substituent; both 4- and 3-substituted phenols gave excellent conversions of 90% (entries 9 and 10), although the 2-substituted phenol gave none of the desired product (entry 11). The ability of the acyl group to chelate to metal centres may be an additional failing of this substrate. The system was also shown to successfully couple electron-withdrawing 4- and 3-cyano substituents; 4-nitro and 4-chloro substituents as well as the electron-donating 3-dimethylamine substituent (entries 12-15 and 17). Unsurprisingly, when attempts were made to selectively couple a hydroxyaniline or a hydroxyindole substrate at the phenolic site in preference to the amine site, a mixture of products was observed (entries 18 and 19). Nucleophilic amines could compete with an alcohol in the substitution step of the palladium catalytic cycle to produce analogous enamine derivatives, giving rise to the observation of multiple products. Reaction with a 2,4-disubstituted phenol also gave rise to multiple products of which no vinylic proton shift was observed, indicating that none of the desired product had been formed. Unfortunately, 2-fluorophenol was the only *o*-subtituted phenol to give a respectable yield of 85% (entry 16).

Finally, the cross-coupling of the parent vinyl triflate with phenol was carried out on a 1 gram (3.5 mmol) scale to give the isolated enol ether in an 85% yield, demonstrating the transferability of the methodology to larger scale processes.

We hoped to curb the disappointing results obtained for the *o*-substituted derivatives by employing an alternative ligand system that had proven to be more efficient in its application to more sterically demanding coupling reactions. Phosphines **6a**, **6b** and **6c**, derived from anthracene, have shown utility for the Suzuki cross-coupling reaction to form sterically hindered tetra-*ortho*-substituted biaryls in excellent yields.[30,32,33] Unfortunately, when applied to our system, none of the desired enol ether was observed.

Poorer yields of certain aryl enol ethers might be attributed to a competing side reaction. Buchwald and Hartwig have provided several examples of the formation of aryl *tert*-butyl ethers in the presence of 2-(di-*tert*-butylphosphino)biphenyl **3b** and di-*tert*-butylphosphinoferrocene **9** ligands employing NaO^tBu as the alkoxide source.[34,35] We therefore carried out a test reaction with our original coupling partner **21** in the absence of the phenol reactant to determine whether or not the formation of a *tert*-butyl enol ether **79** was a competing side reaction (**Scheme 2.10**).



Scheme 2.10 Competing palladium-catalysed alkoxide coupling

The *tert*-butyl enol ether **79** was observed in 70% conversion. Consequently, it would contribute to the inhibition of the reaction if its rate of formation were greater than the rate of formation of the phenolic enol ether.

2.2.3 Variation of vinyl triflate

The vinyl triflates of acetophenone and α-tetralone were prepared using triflic anhydride in moderate yields (entries 1 and 2 respectively, **Table 2.4**). Both delivered the desired enol ether adducts in good yields under the optimised reaction conditions, demonstrating the general applicability of our protocol.

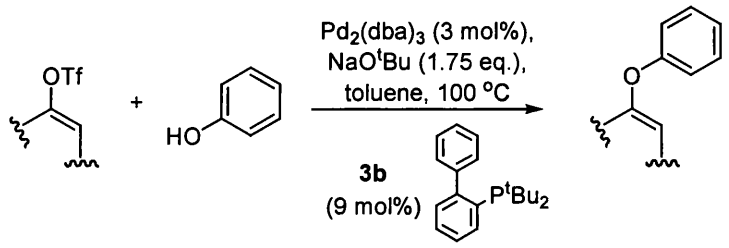
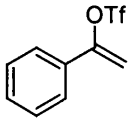
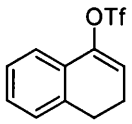


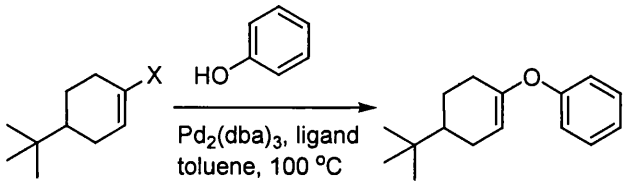
Table 2.4 Triflate scope

Entry	Triflate		Time (h)	Yield (%)	
1		**80a**	22	100	**80b**
2		**81a**	48	78	**81b**

Conditions: triflate (1.0 eq.), phenol (1.5 eq.).

The success and rates of reaction of palladium catalysis also depends upon the ease of oxidative addition across the *C-X* bond. This tends to be a rate-determining step of the cycle (**Scheme 1.7**).[36] Generally, the trend is as follows: -I > -OTf ≅ -Br > -Cl. Therefore, we wanted to compare the analogous halide substrates to determine the best overall system. The vinyl halide substrates **82** were readily prepared from the

corresponding triflate **21** *via* a Stille cross-coupling reaction with hexamethylditin (Sn_2Me_6), and subsequent treatment with bromine or iodine (**Scheme 2.11**).[37, 38,39]



82
X= -Br, -I

64

Scheme 2.11 Proposed synthesis of enol ethers from vinyl halides

Initial studies, however, showed that the optimised conditions for the vinyl triflate to enol ether transformations did not effect the analogous halide cross-couplings. Use of silver triflate as an additive did not improve the results. Palladium-catalysed coupling reactions are notorious for their dependence upon finding the correct combination of reaction variables suggesting that further palladium source/ligand/base combinations would need to be investigated.[31]

2.3 Concluding Comments

In summary, a convenient and high yielding route for the synthesis of aryl enol ethers has been described. The use of readily available alkenyl triflates in combination with electron-rich, electron-poor and electron-neutral phenols, allows a variety of substituted enol ethers to be produced. Finally, given the general nature of the described methodology, we anticipate that it should find application in synthesis.

Since this work was published in 2003, two noteworthy papers have been published highlighting copper-catalysed processes. The first by Ma *et al.* describes a copper iodide (CuI)/*N,N*-dimethylglycine-catalysed cross-coupling reaction of vinyl halides with a range of substituted phenols and 2-iodophenol, demonstrating the successful application of an intramolecular palladium-catalysed cyclisation of enol ethers to give 2,3-disubstituted benzofurans.[40] The second by Li and Fang describes a CuI-catalysed approach to the synthesis of cyclic enol ethers *via* intramolecular *O*-vinylation of alcohols or ketone enolates with vinyl bromides.[41] Both methods employed mild base (Cs_2CO_3 and K_2CO_3 respectively) and moderate temperatures (60-90 °C), tolerating acyclic and cyclic groups as well as halide, ester, alkyl or aryl substituents.

2.4 References

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Chapter 3 Application of Palladium Catalysed *C-O* Bond Formation to the Synthesis of the Benzofuran Motif

An investigation towards an intramolecular variation of our proposed desymmetrisation protocol was undertaken. One of the possible cyclisation modes will involve a key intramolecular palladium catalysed cyclisation step to form a new *C-O* bond to inevitably arrive at the benzofuran substructure. Consequently, new methodology with regards to the synthesis of the benzofuran motif will be detailed below.

3.1 Synthesis of the Benzofuran Motif

The benzofuran motif is present in a large number of naturally occurring molecules and has become fundamentally important; it has been shown to possess key biological function and therefore has potential in pharmacological agents (**Figure 3.1**).[1-8] To date, there are a wide variety of methods for their synthesis, although new methods that allow alternative substrates to be converted into benzofurans are valuable. There are three main bond constructions that have been focussed upon to form the heterocyclic moiety, mainly, the formation of the O-C_2[9-12] or C_2-C_3[13-16] or C_3-C_{3a}[17-20] bonds. In this chapter we will outline a new method that involves the formation of the O-C_{7a} bond.[21]

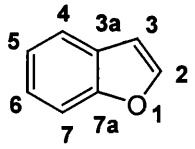
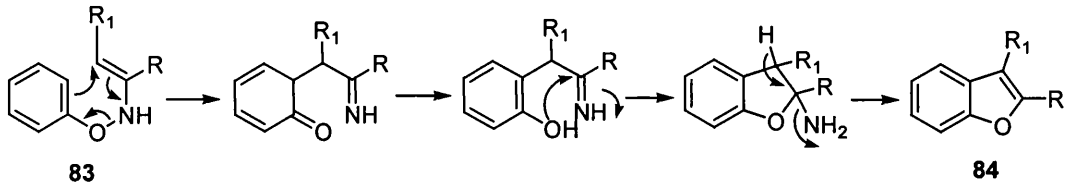


Figure 3.1 Benzofuran motif

A few representative examples for the formation of benzofurans are described from the latter end of the century, highlighting a range of different bond formations for their construction by employment of traditional and modern chemistry.

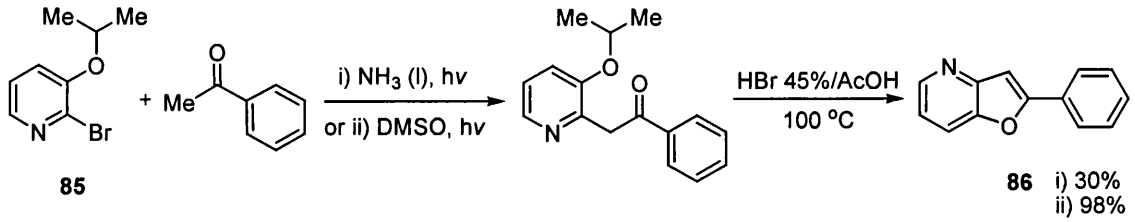
Non-metal mediated syntheses

One of the earlier methods reported for the synthesis of benzofurans exploits the thermal rearrangement of *o*-phenyl oximes **83** by a pathway analogous to the Fischer indole synthesis; the oxime undergoes rearrangement, aromatisation to a phenol with subsequent nucleophilic attack of the hydroxyl on the amine to give the benzofuran **84** (**Scheme 3.1**).[22] This methodology has also been successfully applied to *o*-(2-pyridyl) oximes to give the corresponding furo-pyridine analogues.



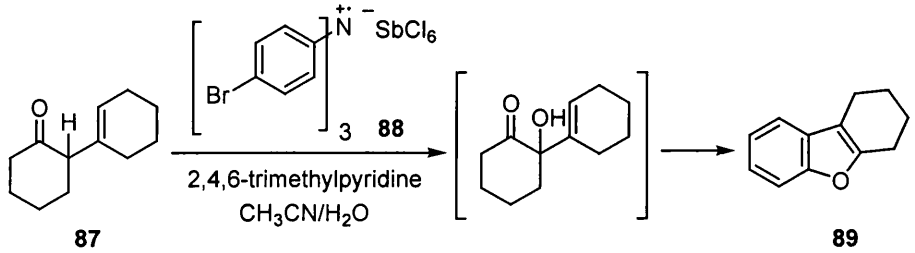
Scheme 3.1 Thermal rearrangement of oxime to benzofuran

Bois-Choussy and Beugelmans also reported the synthesis of furo-pyridyl compounds, making use of photostimulation methodology (**Scheme 3.2**).[23] Hydroxypyridines **85**, containing a leaving group in the *ortho*-position and an isopropyl protection on the phenol, are employed as the starting materials for this S_NAr substitution reaction. In many cases, standard photostimulation conditions can be modified by the replacement of liquid ammonia with DMSO to achieve the α-arylation at ambient temperature. A terminal acid catalysed deprotection and condensation reaction can be executed cleanly to give the furo[3,2-*β*]pyridines **86** in quantitative yield. Simple alkyl and aryl substituents on the ketone substrate were tolerated well.



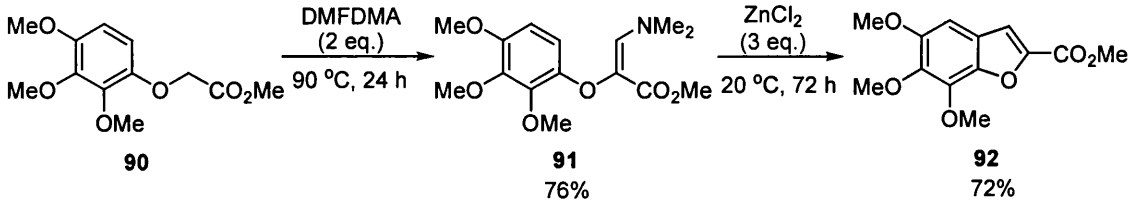
Scheme 3.2 Synthesis of furo[3,2-*β*]pyridines *via* an S_NAr reaction

Alternative, chemically induced radical reactions have been developed by the group of Schultz (**Scheme 3.3**).[24,25] They detailed the α-oxidation of ketones using radical cation salts of triarylamines **88** and the application of this strategy to an isolated example employing ketone **87**, produced the corresponding benzofuran **89** in quantitative yield.[26] From this example, they postulated a mechanism for the α-oxidation proceeding *via* a cationic intermediate involving electron transfer from the initially formed enol tautomer. Applicability of this method has not been studied further.



Scheme 3.3 α-Oxidation of ketone with immediate cyclisation

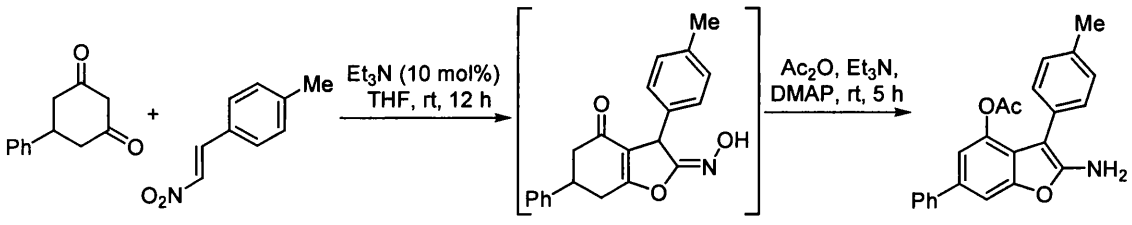
Although each of these methodologies gave the desired benzofurans, more general protocols were sought. A recent report by Tamariz described a more general approach towards the synthesis of 2-methoxycarbonylbenzofurans **92** (**Scheme 3.4**). Treatment of phenoxyacetic methyl ester substrates **90** with *N,N*-dimethylformamide dimethyl acetal at 90 °C over 24 hours provided the intermediate 2-aryloxy-3-dimethylaminopropenoates **91** as single stereoisomers with *Z*-configuration.[27] Direct heating in acetonitrile at 100 °C promoted the cyclisation of activated propenoates bearing electron-donating subtituents. Alternatively, employing zinc chloride as a Lewis acid to promote this Michael-type addition allowed for the cyclisation to be carried out at ambient temperatures, although longer reaction times were required. A one-pot procedure was achieved by direct treatment of the phenoxyacetic methyl esters **90** with DMFDMA in acetonitrile at 100 °C. Prolonged reaction times of 48 hours were necessary and unfortunately, lower yields were attained.



90 **91** 76% **92** 72%

Scheme 3.4 Cylisation of 2-aryloxy-3-dimethylaminopropenoates

Highly substituted 4-Acetoxy-2-amino-3-arylbenzofurans **95** have been prepared from cyclohexane-1,3-diones **93** and 1-aryl-2-nitroethylenes **94** in a one-pot two-step approach by Ishikawa *et al.* (**Scheme 3.5**).[28] The proposed mechanism involves a sequence of 13 elementary reactions beginning with a Michael addition reaction initiated by a catalytic amount of triethylamine in THF at room temperature. After 12 hours, the expected cyclic oxime intermediate **I** was reacted with stoichiometric acetic anhydride, triethylamine and 4-(*N,N*-dimethylamino)pyridine to yield the benzofuran product **95**.



93 **94** **I** **95** 76%

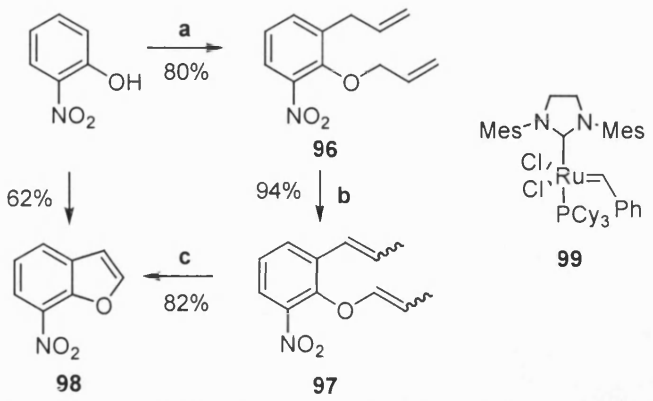
Scheme 3.5 One-pot synthesis of highly substituted benzofurans

A number of symmetrical cyclohexane-1,3-diones were successfully coupled with a range of methoxy-/nitro- or halo-substituted 1-aryl-2-nitroethylenes in moderate to excellent yields.

Metal-mediated syntheses

In 1984, Larock described the synthesis of benzofurans and related heterocycles *via* the intramolecular solvomercuration of aryl acetylenes.[29] The process required a stoichiometric mixture of mercuric acetate in acetic acid at ambient temperature to initiate an alkoxymercuration of the acetylene to give the desired benzofurans in moderate yield. The use of mercury in any process is undesirable and, since this publication, alternative metal-based catalysts have been developed to overcome this issue.

In 1994 Grubbs *et al.* reported the synthesis of 2-substituted benzofurans employing a titanium-mediated ester alkylidenation followed by molybdenum alkylidene-catalysed ring-closing metathesis (RCM).[30] However, development of ruthenium-based catalysts for RCM delivered new reactivity and subsequently new procedures.[31,32] **Scheme 3.6** demonstrates one such protocol that involves application of a ruthenium-based catalyst for an isomerisation-ring-closing metathesis strategy for the synthesis of aryl-substituted benzofuran analogues **98**.[33] A number of substituted phenols were allylated with subsequent microwave promoted Claisen rearrangement to give *o*-allylated phenol intermediates with a second allylation providing the corresponding 1-allyl-2-allyloxybenzenes **96**. The isomerisation of the mixed *C*- and *O*-allyl system was completed employing the established $[RuClH(CO)(PPh_3)_3]$ catalyst with the resulting aryl enol ethers **97** being used directly in the next reaction.[34] The key RCM reaction was moderately successful employing the second-generation Grubbs catalyst **99**, with yields ranging from 20-100% being attained.

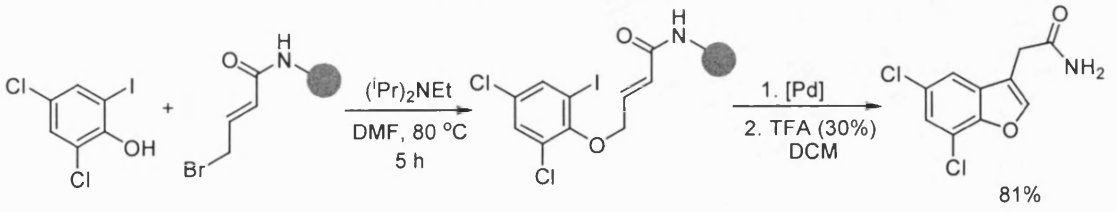


Conditions: **a**: 1) K_2CO_3, allyl bromide, acetone; 2) microwave irradiation, neat, 100 W, 180-220 °C; 3) K_2CO_3, allyl bromide, acetone; **b**: $[RuClH(CO)(PPh_3)_3]$ (5 mol%), toluene; **c**: catalyst **99** (5 mol%), toluene.

Scheme 3.6 Ring-closing metathesis strategy

Palladium-mediated syntheses

In 1997, Zhang described a new solid phase methodology for the synthesis of small molecules employing Rink amide AM resin and a key palladium catalysed intramolecular Heck cyclisation reaction (**Scheme 3.7**).[35] Adapting an already useful solution phase reaction to solid support gives the chemist an alternative route to the substituted benzofuran motif and the production of libraries of small molecules.



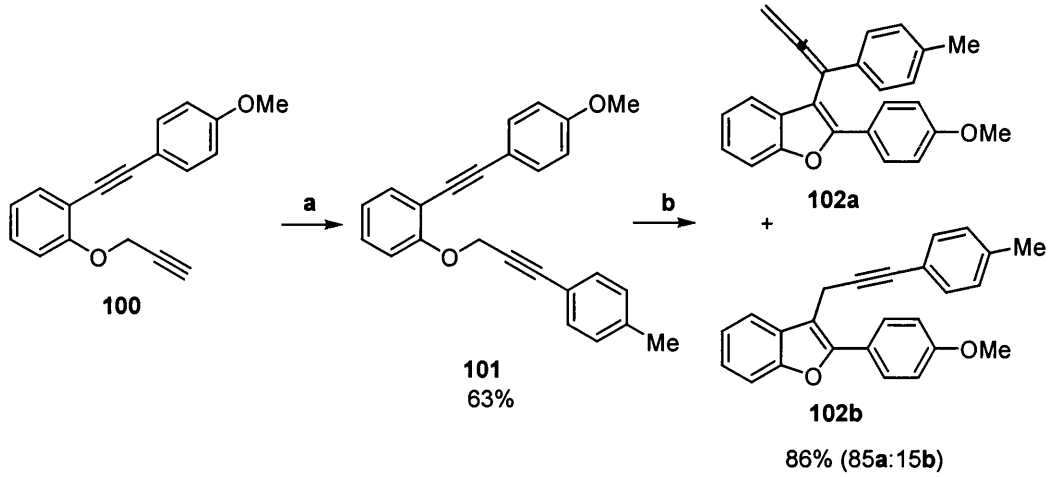
Conditions: [Pd]: $Pd(PPh_3)_2Cl_2$, Bu_4NCl, Et_3N, DMF-H_2O (9:1), 80 °C, 24 h.

Scheme 3.7 Solid phase approach to the synthesis of the benzofuran motif

Other procedures have been developed that involve manipulation of the starting substrates through to the product benzofuran whilst bound to a resin *eg.* TentaGel or Wang.[36] Ley also reported a solid phase strategy, employing polymer-supported reagents to manipulate a range of ketones to give 3-phenyl and 3-aminobenzofurans.[37]

Over the last decade, the groups of Cacchi[38] and Arcadi have established the role of organopalladium complexes for the intramolecular cyclisation of proximate nulceophiles onto the triple bond of alkyne functional groups.[39-41] **Scheme 3.8** depicts an extension of their early methodology to the cyclisation of propargylic *o*-(alkynyl)phenyl ethers[42] which is complimentary to the cyclisation of allylic *o*-(alkynyl)phenyl ethers. The starting propargylic *o*-(alkynyl)phenyl ethers **100** were

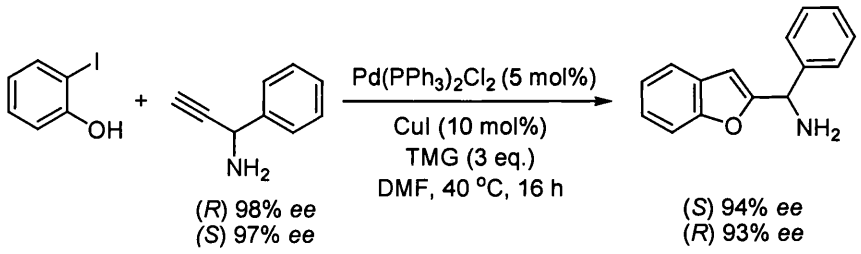
synthesised from the analogous *o*-(alkynyl)phenol derivatives with an additional palladium catalysed reaction being employed to functionalise the terminal alkyne. The cyclisation conditions employed were the same as for the allylic substrates [$Pd(PPh_3)_4$, K_2CO_3 in DME] although increased temperatures were required (typically 110 °C). It was found that the presence of a substituent on the terminal alkyne **101** was crucial for the success of the construction of the 3-allenyl-2-substituted benzo[*β*]furans **102a/b**.



Conditions: **a**: *p*-Me-C_6H_4-I, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 40 °C, 3 h; **b**: $Pd(PPh_3)_4$, K_2CO_3, DME, 110 °C, 36 h.

Scheme 3.8 Palladium-catalysed cyclisation of propargylic *o*-(alkynyl)phenyl ethers

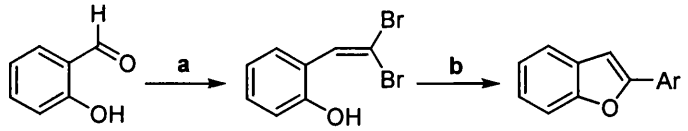
There have been numerous citations reporting the direct intramolecular cyclisation of the phenolic oxygen onto the triple bond of an alkyne without the need for a protecting group.[43-46] One-pot procedures have emerged with the initial alkynylation of an *o*-halophenol derivative being catalysed under Sonogashira type palladium catalytic conditions with subsequent cyclisation of the phenol.[47] Botta, Corelli and coworkers have carried out a desirable *enantio*-enriched one-pot alkynylation and annulation of an intermediate α-arylpropargylamine, again, employing Sonogashira type conditions [$Pd(PPh_3)_2Cl_2$, CuI] (**Scheme 3.9**).[48] No undesirable cross-coupling of the free amine with the aryl iodide was observed.



Scheme 3.9 One-pot tandem palladium-catalysed alkylation/cyclisation

Many one-pot procedures elaborate further, incorporating palladium catalysed carbonylations of the intermediate organopalladium benzofurans to give functionalised 3-substituted benzofuran adducts.[49-51] Hu, Fathi and Yang *et al.* have described a unique combinatorial approach to prepare conformationally restricted 2,3-diarylbenzo[β]furans by the palladium catalysed annulation of *o*-alkynylphenols.[52] A three-component coupling was exploited with the iodophenol portion attached to a high-capacity polystyrene macrobead, coupling stepwise with a range of terminal acetylenes and aryl iodides to give a library of 2,3-diarylbenzo[β]furans. The resulting compounds were used in biological assays without further purification, demonstrating the effectiveness of this combinatorial approach.

Other groups pursued alternative synthetic approaches in a bid to extend the use of palladium chemistry in this area. Previously, 1,1-dibromoalkenes have demonstrated versatility in palladium catalysed cross-coupling reactions of boronic acids (Suzuki)[53] and organostannanes (Stille).[54,55] More recently, Bisseret *et al.* have shown it to be a successful functional group when employed in a tandem one-pot palladium catalysed cyclisation-coupling reaction to form 2-substituted benzofurans (**Scheme 3.10**).[56]



Conditions; **a**: 1) NaH, DMF then MOMCl, 12 h, rt, 40%, 2) CBr_4, PPh_3, Zn, CH_2Cl_2, 12 h, rt, 70%; **b**: $Pd(OAc)_2$, dppf, Et_3N(3 eq.), toluene, 100 °C, Ar coupling reagent: $ArSnMe_3$ or $ArB(OH)_2$

Scheme 3.10 Tandem one-pot palladium-catalysed cyclisation-coupling of 2-hydroxy benzaldehyde

Original work towards the preparation of new aromatic alkynylphosphonates by a palladium catalysed coupling reaction between 1,1-dibromoalkenes and diethylphosphite employing methodology reported by Lera and Hayes,[57] [$Pd(OAc)_2$, dppf or TFP, propylene oxide as a HBr scavenger, DMF, Δ] provided the desired alkynylphosphonate and the unexpected 2-(diethylphosphonyl)-benzo[β]furan. Optimisation of the conditions found triethylamine and toluene to be the base and solvent of choice. Adaptation of the reaction by substituting the coupling partner, diethylphosphite for either trimethyl(phenyl)tin (Stille coupling) or *p*-methoxyphenylboronic acid or ester (Suzuki coupling) provided the desired 2-arylsubsitituted benzofurans in good yield. An excess of reagents was required to

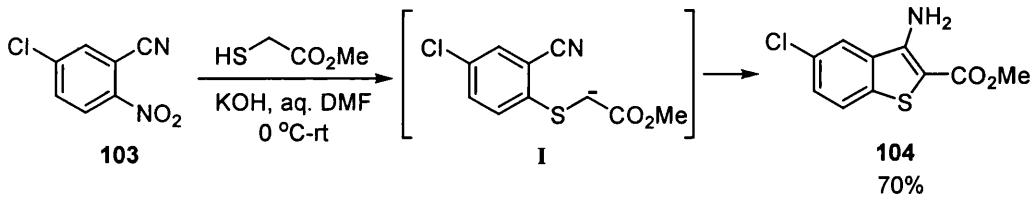
suppress the formation of a homo-coupled dibenzofuran by-product with none of the alkyne product being observed.

3.2 Synthesis of the benzothiophene motif

The benzothiophene motif differs only to the benzofuran motif by a sulfur atom in place of the oxygen atom. Unsurprisingly, the benzothiophene motif is an important substructure as it too exists in many biologically active molecules, exhibiting potent pharmacological activity; therefore, new methods are continually sought for their preparation.[58,59]

Non-metal mediated syntheses

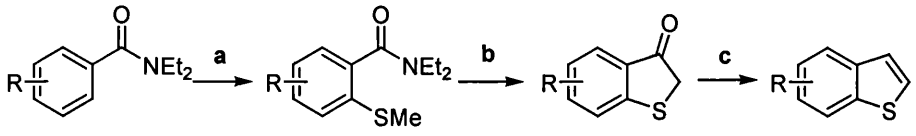
One of the earliest methodologies for its preparation was outlined by Beck in 1972, describing the direct synthesis of benzo[β]thiophene-2-carboxylate esters **104** (**Scheme 3.11**). The key step takes advantage of the lability of a nitro group *ortho-* to a cyano or carboxaldehyde function **103** in an intermolecular S_NAr reaction by methyl thioglycolate. Subsequent base catalysed cyclisation of the thiomethine moiety **I** onto the adjacent cyano group gives the substituted benzo[β]thiophene **104**. Unfortunately, the reaction scope was limited and gave only reasonable yields for the halide substituted nitroaryl substrates **103**.



Scheme 3.11 Benzo[β]thiophenes *via* base-catalysed cyclisation

A few years later, De *et al.* described a comparable directed metalation approach to the formation of aryl-substituted benzo[β]thiophenes (**Scheme 3.12**).[60] They first introduced a methylsulfanyl group into the *ortho* position of a substituted benzylamide **105** and with its subsequent deprotonation, initiated intramolecular nucleophilic attack onto the amide. Final reduction of the newly formed thioindoxyl intermediate **106** gave the desired benzo[β]thiophenes **107.** Excellent yields were attained for all steps of the reaction sequence, tolerating a number of functional groups, although an anomaly was evident with the attempted sodium borohydride reduction of the chloro-substituted thioindoxyl. Reduction of the thioindoxyl should involve initial formation of a carbinol

derivative followed by dehydration, instead, they isolated the carbinol derivative, 2,3-dihydro-3-hydroxy-4-chloro benzo[*β*]thiophene.

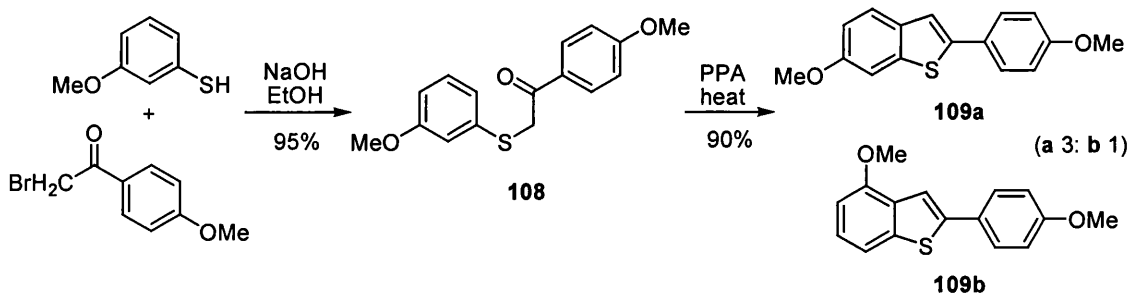


	105	**106**	**107**
R=H	77%	67%	67%
R=(2,3)-OMe	72%	89%	73%
R=2-Cl	75%	68%	0%

Conditions: **a**: *sec*-BuLi (1.1 eq.), -78 °C, SMe_2 (2 eq.), rt, 5 h; **b**: LDA (2.5 eq.), rt, spontaneous; **c**: $NaBH_4$ (2 eq.), 10% NaOH/MeOH, reflux, 1 h then simmer for 12 h.

Scheme 3.12 Directed metalation approach to give substituted benzo[*β*]thiophenes

Several reports in the literature echo the approach outlined in **Schemes 3.11** and **3.12**, forming the benzothiophene ring *via* base promoted nucleophilic cylisation reactions to give benzo[*β*]thiophene-2-carboxylates,[61,62] 3-amino and 3-hydroxy-thieno[2,3-*β*]pyridines[63,64] and 2-aryl-3-hydroxybenzo[*β*]thiophenes.[65] In addition, Hartley and Roberts reported the successful application of solid supported titanium(IV) benzylidenes (Schrock carbenes) bearing masked sulfur nucleophiles to afford 2-substituted benzo[*β*]thiophenes upon deprotection and subsequent cyclisation.[59] Complementary electrophilic cylisation strategies are known with one such strategy being employed to obtain the Raloxifene® intermediate, 6-methoxy 2-(4-methoxyphenyl)benzo[*β*]thiophene **109a** (**Scheme 3.13**).[58] The nucleophilic substitution reaction involving 3-methoxybenzene thiol and bromoacetophenone afforded sulfide **108** in excellent yields. Cyclisation with simultaneous aryl ring migration in the presence of polyphosphoric acid (PPA) gave a mixture of regioisomers **109a** and **109b**. Employment of Friedel-Crafts methodology gave the requisite benzothiophene ligands that are designed to interact with tubulin and stop the development of solid-tumor-type cancer cells.

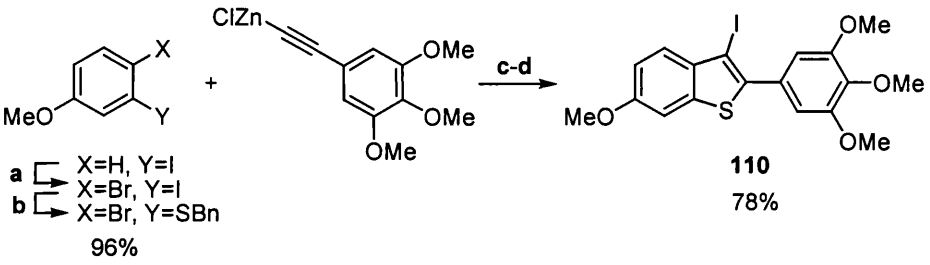


Scheme 3.13 Part synthesis of Raloxifene®

Palladium-mediated syntheses

Thus far, fewer palladium-catalysed strategies for the preparation of benzo[*β*]thiophenes exist in comparison with their benzofuran counterparts. Not surprisingly, the few methods published, have been developed from the palladium-catalysed *C-O* bond formation strategies, the most prevalent of which is the intramolecular cyclisation of protected *o*-ethynylphenyl thiols to access 2,3-disubstituted benzo[*β*]thiophenes (*cf.* cyclisation of *o*-ethynylphenyl phenols).

The group of Larock reported a mixed palladium-copper catalysed coupling of *o*-iodoanisole and terminal alkynes, with subsequent electrophilic cyclisation by a range of electrophiles to give 2,3-disubstituted benzo[*β*]thiophenes in excellent yields.[66] A more versatile method was reported shortly afterwards by Flynn *et al.* employing a substituted mixed 1,2-dihalobenzene as starting substrate to give more highly substituted 2,3-disubstituted benzo[*β*]thiophenes (**Scheme 3.14**).[67]



Conditions: **a**: NBS, DMF, 80 °C, 4 h; **b**: $Pd(dba)_2$ (3 mol%), dppf (3 mol%), BnSH, DMF, Et_3N, 70 °C, 3 h; **c**: $Pd(PPh_3)_2Cl_2$ (2 mol%), PPh_3 (4 mol%), DMF, 100 °C, 3 h; **d**: I_2, DCM.

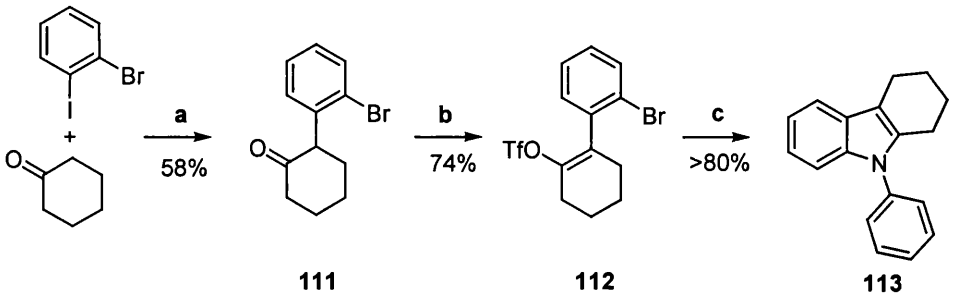
Scheme 3.14 Formation of 2,3-disubstituted benzo[*β*]thiophenes

Although the majority of the steps involve palladium catalysis, the key cyclisation step involves formation of a 3-iodobenzo[*β*]thiophene **110** *via* a 5-*endo-dig* iodocyclisation of the intermediate benzyl *o*-ethynylphenyl sulfide in the presence of iodine. A final palladium catalysed cross-coupling can be effected at the 3-position to give further substitution on the ring. Flynn developed this strategy further, applying it to the formation of 2-acyl- or 2-(1-iodoalkenyl)-benzo[*β*]thiophenes from readily accessible propynols with a 2-thioxyphenol substituent only in this instance, *via* a 5-*exo*-iodocyclisation mechanism.[68]

3.3 A Novel *O*-Enolate Cyclisation

Discovery

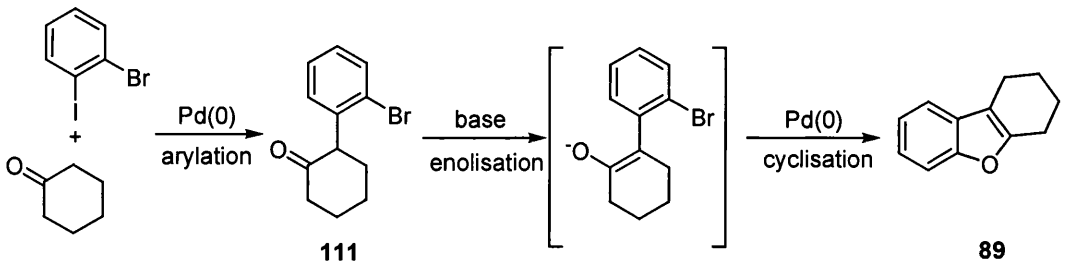
An investigation towards a novel palladium catalysed tandem alkenyl and aryl *C-N* bond forming reaction to yield 1-functionalised indoles was being carried out within the Willis laboratory by Gareth Brace (**Scheme 3.15**).[69] The chosen precursor for these studies was an α-arylated enol triflate **112** which can be readily prepared by triflation of the corresponding α-arylated ketone **111**. A double palladium catalysed cross-coupling reaction between α-arylated enol triflate **112** and a range of primary amines was successfully carried out with excellent yields being achieved.



Conditions: **a**: $Pd_2(dba)_3$ (0.5 mol%), Xantphos (1.2 mol%), Cs_2CO_3 (2.2 eq.), dioxane, 80 °C, 24 h; **b**: NaH, *N*-phenyl-*bis*(trifluoromethanesulfonimide), DMF, 0 °C-rt, 24 h; **c**: $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6.0 mol%), Cs_2CO_3 (2.2 eq.), toluene, aniline, 100 °C.

Scheme 3.15 Novel palladium-catalysed formation of indoles

When establishing conditions for the palladium catalysed α-arylation of cyclohexanone to give ketone **111** he discovered trace amounts of an unknown product. Ultimately, the unknown was characterised and found to be 1,2,3,4-tetrahydrobenzo[*β*]furan **89** (**Scheme 3.16**).



Scheme 3.16 Novel Pd catalysed *O*-enolate cyclisation

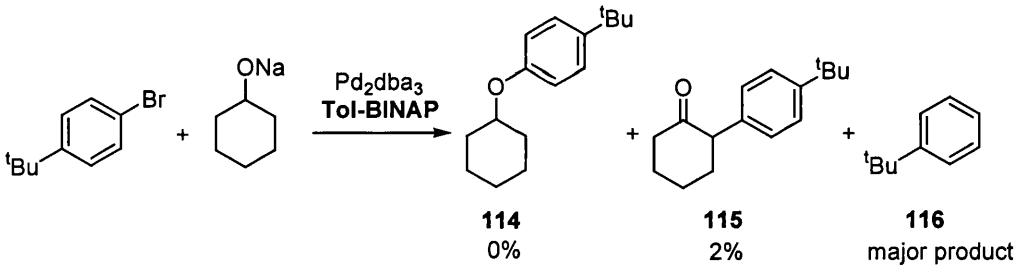
The direct conversion of 1-(2-halo-aryl)ketones into the corresponding benzofurans employing palladium catalysis has not been reported and would therefore compliment the known methodologies described in the literature.[49] The key step is thought to involve the coupling of an oxygen atom of an enolate with a halo-substituted arene ring.

It is this characteristic palladium catalysed *C-O* bond forming reaction that we have explored and the results of which lie herein.

3.3.1 α-Arylation of Ketones

To establish the generality of this palladium catalysed *O*-enolate cyclisation, we first have to synthesise a range of α-arylated ketones. Early literature methods involved; S_N2 substitution of α-haloketones by nucleophilic arene substrates,[70] photoinduced S_N1 reactions,[71] the use of stoichiometric amounts of tunable arylating reagents,[72] $Ni(COD)_2$ catalysis for the intramolecular cross-coupling reaction between aryl iodides and ketone enolates and nickel and palladium-catalysed intermolecular cross-coupling reactions that unfortunately required stoichiometric amounts of tin reagents. Over the last decade, a general method was discovered to afford α-arylated ketones in high regioselectivity from readily available starting materials.

The palladium-catalysed α-arylation of ketones was discovered concurrently within the laboratories of Buchwald (**Scheme 3.17**)[73] and Hartwig[74] as a secondary reaction when they were striving to realise novel palladium catalysed *C-O* and *C-N* bond formations respectively.

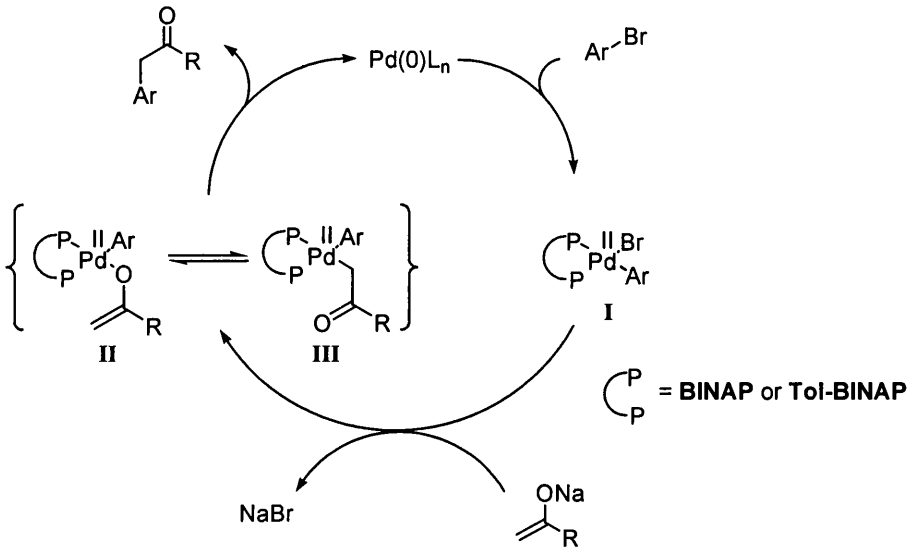


Scheme 3.17 α-Arylation of cyclohexanol salt

The palladium-catalysed arylation of the sodium salt of cyclohexanol (**Scheme 3.17**) was carried out in an attempt to afford the *C-O* bond formation product **114**, however, the reaction gave the reduced arene **116** as the major product with simultaneous oxidation of the desired alcohol product to give the corresponding ketone. Subsequent exposure of the ketone to the catalyst gave the α-arylated ketone **115** in trace amounts. Further development of the catalytic conditions led to an optimal combination of reagents: $Pd_2(dba)_3$ (3 mol%), (*rac*)-BINAP or Tol-BINAP (3.6 mol%) as the ligand with NaO^tBu (1.5 eq.) as the base in THF at elevated temperatures. The group of Hartwig discovered an alternative combination of reagents, typically; $Pd(dba)_2$ (7.5 mol%), dtpf **12d** (9 mol%) as the ligand and $KN(SiMe_3)_2$ (2.2 eq.) as the base, again in

refluxing THF.[74] Both gave moderate to excellent yields of the desired α-arylated ketones by cross-coupling a range of *o*-, *m*- and *p*-substituted aryl halides with α,*β*-substituted ketones.[75]

Scheme 3.18 depicts a proposed palladium catalytic cycle for the α-arylation of ketones. Initial oxidative addition of the $Pd(0)L_n$ with the aryl bromide substrate gives the Pd(II) organometallic intermediate **I**. Nucleophilic substitution of the bromide by the sodium enolate provides both Pd(II) organometallic intermediates **II** and **III** which can undergo reductive elimination to yield the desired α-arylated ketone, regenerating the $Pd(0)L_n$. There was no evidence of *β*-hydride elimination suggesting that the intermediates had been rendered four co-ordinate by the bidentate BINAP ligands.



Scheme 3.18 Proposed mechanism for palladium-catalysed α-arylation of ketones

Table 3.1 depicts a representative selection of the known examples, both inter- and intramolecular variants have been reported.[76,77] The majority of the early examples cited involve cross-couping between an arylbromide and ketone to give the corresponding α-arylated ketone.

The general combination of reagents: palladium source, ligand, base and solvent at elevated temperatures holds true for all of the examples shown, however, the specific combination of these reagents does not. Individual and groups of reactions rely upon a unique combination of reagents to attain excellent yields and in some cases, more than one combination has proven successful (entries 1 and 2). In general, bulky, electron rich phosphine ligands are suitable partners for the catalyst, although other types of ligands have been successful eg. carbenes.[78]

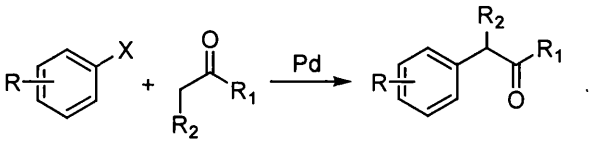
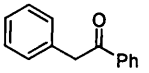
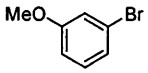
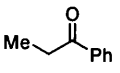
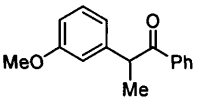
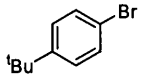
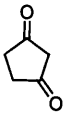
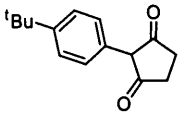
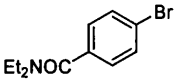
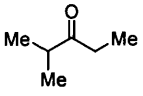
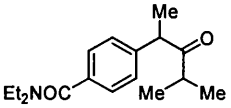


Table 3.1 α-Arylation of ketone enolates

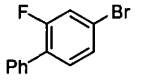
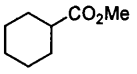
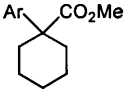
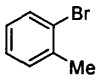
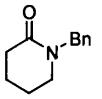
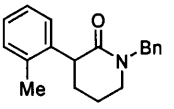
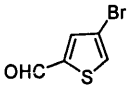
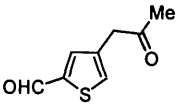
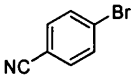
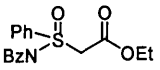
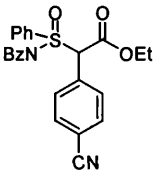
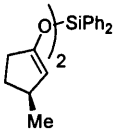
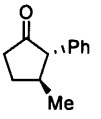
Entry	Ref	Halide	Ketone	Ligand	Base	Product	Yield (%)
1	74			dtpf, **12d**	$KN(SiMe_3)_2$		84[a,b]
2	73			(*rac*)-BINAP	NaO^{t}Bu		91[c,d]
3	75			**5b**	K_3PO_4		96[e]
4	75			Xantphos	NaO^{t}Bu		74[f]

Conditions: **a**: $Pd(dba)_2$ (7.5 mol%), ligand (9 mol%), base (2.2 eq.), THF, reflux, 45 min.; **b**: alternative ligand: dppf **12c**; **c**: $Pd_2(dba)_3$ (1.5 mol%), ligand (3.6 mol%), base (1.3 eq.), THF, 70 °C, 18 h; **d**: alternative ligands: d^{t}bpf **12b**, $P(^tBu)_3$, PCy_3, **3b**; **e**: $Pd(OAc)_2$ (1 mol%), ligand (2.2 mol%), base (2.3 eq.), THF, 80 °C, 23 h; **f**: $Pd_2(dba)_3$ (1 mol%), ligand (2.2 mol%), base (2 eq.), 80 °C, toluene, 15 h.

Table 3.2 depicts only a few of the different types of α-arylations that have been successful to date. Palladium-catalysed α-arylations[79] of aldehydes,[80,81] malonates,[82-84] esters (entry 1, **Table 3.2**),[85-88] amides,[88,89] piperidinones (entry 2),[90] acetone analogues (entry 3),[91] protected amino acids,[92] nitriles,[89,93] nitroalkanes,[75] sulfoximes (entry 4)[94,95] and asymmetric equivalents[96-98] have recently been established.

Despite this generality α-arylations of cyclopentanone have yielded poor conversions, however, Buchwald recently reported a fluoride promoted arylation of a silyl enol ether adduct of cyclopentanone (entry 5) employing enantiomerically enriched diphenylsilyl enol ethers, prepared from a copper-catalysed asymmetric conjugate reduction of cyclopentanone.[99] This approach has been used to overcome several problems that may arise due to the increased reactivity of the applied ketone. Limitations such as: multiple arylation,[100] racemisation of the newly formed tertiary centre or formation of aldol products. A one-pot protocol also gave reasonable yields and high *ee*'s.

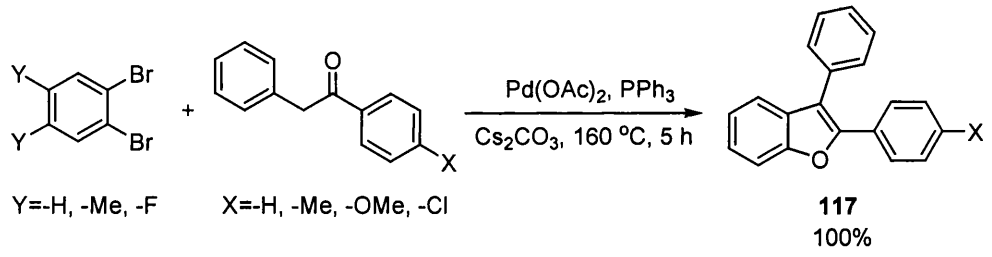
Table 3.2 Novel categories of palladium-catalysed α-arylations

Entry	Ref	Halide	Ketone Equivalents	Pd Source	Ligand	Base or Additive	Product	Yield (%)
1	89			$Pd(dba)_2$	$P(^tBu)_3$	$LiNCy_2$		90[a]
2	90			$Pd(dba)_2$	Dave-phos, **4a**	*s*-BuLi		83[b]
3	91			$Pd_2(dba)_3$	**4c**	Bu_3SnOMe		88[c]
4	94			$Pd(OAc)_2$	PCy_3	NaO^tBu		90[d]
5	99			$Pd(OAc)_2$	**3b**	CsF		91[e] 93[f]

Conditions: **a**: Pd (0.5 mol%), ligand (0.5 mol%), base (1.3 eq.), toluene, rt, 18 h; **b**: two step 1) base (2 eq.), $ZnCl_2$ (2.2 eq.), -20 °C, 2) Pd (5 mol%), ligand (7.5 mol%), THF, 65 °C; **c**: Pd (10 mol%), ligand (40 mol%), Bu_3SnOMe (1.2 eq.), toluene, 100 °C; **d**: Pd (3 mol%), ligand (9 mol%), base (3 eq.), dioxane, reflux, 1 h; **e**: Pd (5 mol%), ligand (10 mol%), base (1.1 eq.), THF, rt, 18 h; **f**: Enantiomeric excess.

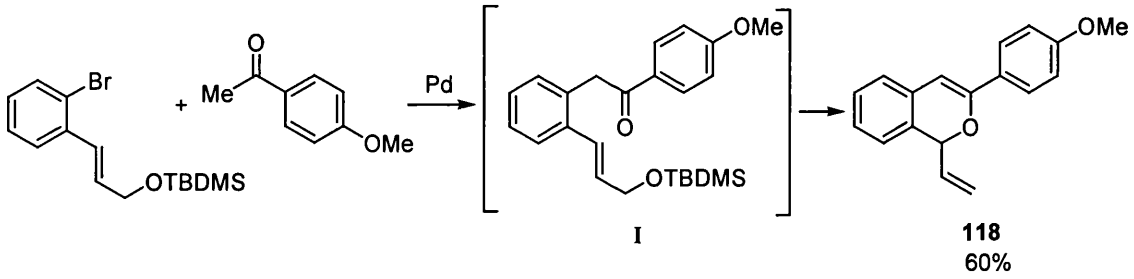
3.3.2 Tandem α-arylation and *O*-enolate cylisation methodology

All of the examples mentioned thus far focus on the coupling of monohaloaryl substrates (-I, -Br and –Cl[101,102]) and it was not until 1999 that Miura *et al.* reported the palladium-catalysed cross-coupling between carbonyl and phenolic compounds with readily available *o*-dibromobenzenes (**Scheme 3.19**).[103,104] They expected to observe a double *C-C* bond formation as a consequence of α- and *ortho*-arylation reactions proceeding in tandem to give a six-membered cyclic ketone. Instead, the consecutive formation of *C-C* and *C-O* bonds *via* a suggested α-arylation and *O*-enolate cyclisation prevailed, to give an unexpected 2,3-diphenylbenzo[*β*]furan product **117** in quantitative yields. Unfortunately, employment of a dibromobenzene substrate does not allow for the control of regioselectivity within the reaction and the use of elevated temperatures limits the scope of available substrates.



Scheme 3.19 Tandem α-arylation and intramolecular *O*-enolate cyclisation

Following in 2000, Wills *et al.* applied the α-arylation methodology to the formation of 1-vinyl-1*H*-isochromene derivatives **118** (**Scheme 3.20**).[105] They originally envisaged the reaction occurring in two key stages. The first involving the α-arylation of an appropriate arylbromide and the second involving the replacement of the silyl group with an acyl group to encourage the subsequent cyclisation of the ketone enolate onto the allylic system. The application of Harwig's conditions [Pd/dppf **12c**, NaO^{t}Bu, toluene, 100 °C][74] gave the debrominated product only, although simple substitution of the base for LiHMDS led to a one-pot preparation of the desired isochromene **118**. Fine tuning of the reaction conditions allowed for the selective formation of the intermediate ketone **I** with employment of P(^{t}Bu)$_3$ or the bis(diazaphospholidine) ligand semi-ESPHOS. They elucidated that the *O*-enolate cyclisation was indeed catalysed by the palladium catalyst with the silyloxy group proving crucial to its success. The unusual leaving group seemed to suitably delay the allylic reaction until after the arylation process was completed, thus, reducing side reactions. A combinatorial approach was employed and an array of isochromenes successfully synthesised.[106]



Conditions: Pd: $Pd_2(dba)_3$ (5 mol%), (2-Ph)$C_6H_4P(^tBu)_2$ (10 mol%), LiHMDS (3 eq.), DME, Δ

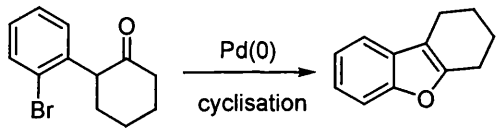
Scheme 3.20 Tandem α-arylation and intramolecular *O*-enolate substitution

Negishi *et al.* have also reported the intramolecular trapping of an acylpalladium derivative with an *O*-enolate *via* a tandem carbonylation/cyclisation reaction.[107] Overall, this methodology has gained wide acceptance and, as a consequence, has been used effectively in the total synthesis of highly complex molecules.[108-110]

Preliminary studies towards palladium-catalysed α-arylation of cyclic and acyclic ketones with mixed 1,2-dihalides to afford several α-arylated ketones were carried out within the Willis laboratory in collaboration with Gareth Brace.

3.4 Cyclisation and formation of Benzofurans

To investigate the proposed intramolecular palladium catalysed *O*-enolate cyclisation we chose to employ α-arylated ketone **111** possessing an *ortho*-bromide to function as our initial *C-X* coupling partner. Preparation of the intermediate (2-haloaryl)-substituted ketone **111** was effected by employing a Xantphos derived palladium catalyst in combination with a mild base, Cs_2CO_3, to mediate the α-arylation of cyclohexanone with 1-bromo-2-iodobenzene (**Scheme 3.16/3.21**). The dihalobenzenes, diiodobenzene and dibromobenzene, were also employed, however, 1-bromo-2-iodobenzene proved the most effective. Trace amounts of the benzofuran product were observed. Unfortunately, when we resubjected α-arylated ketone **111** to a catalyst derived from Xantphos in combination with Cs_2CO_3 we could only isolate small amounts of the benzofuran product (entry 1, **Table 3.3**).



111 **89**

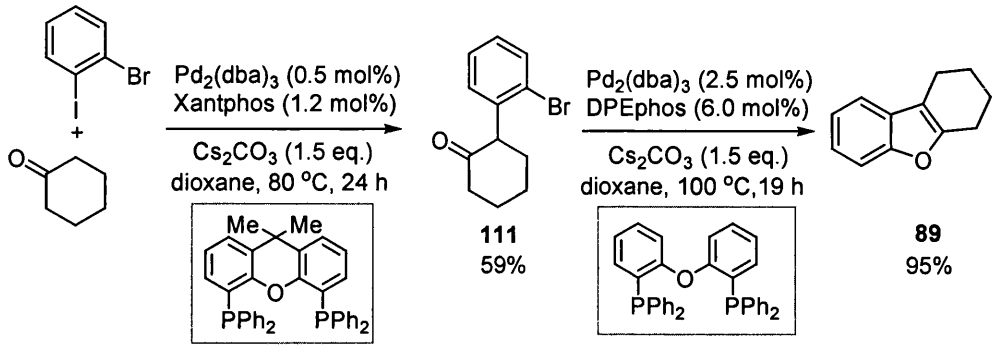
Table 3.3 Optimisation of Benzofuran synthesis[a]

Entry	Ligand	Base	Temp. (°C)	Time (h)	Yield[b] (%)
1	Xantphos	Cs_2CO_3	110	20	<5
2	Xantphos	NaO^{t}Bu	110	20	0
3	DPEphos	Cs_2CO_3	100	20	95
4	DPEphos	Cs_2CO_3	80	24	52
5	DPEphos	Cs_2CO_3	50	30	0

Conditions: **a**: $Pd_2(dba)_3$ (2.5 mol%), ligand (6 mol%), base (1.5 eq.); **b**: Isolated yields.

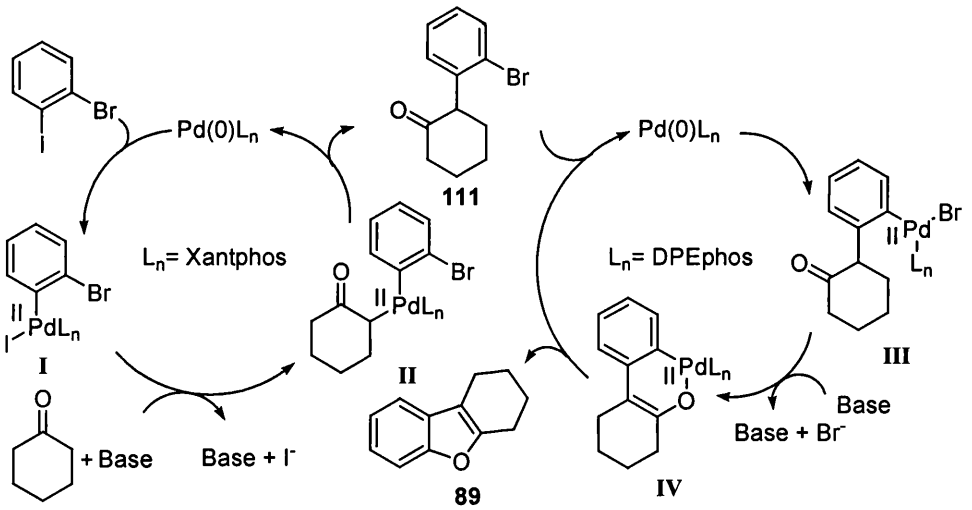
When the same catalyst system was employed with a stronger base no product was obtained suggesting a ligand effect was operating (entry 2). Simple substitution of the ligand Xantphos for the structurally similar ligand DPEphos with Cs_2CO_3 as base provided benzofuran **89** in 95% yield (entry 3). An optimum temperature of 100 °C was required as lower conversions were attained as a consequence of lowering the temperature (entries 4 and 5).

Scheme 3.21 depicts the optimised palladium catalysed two-step reaction to form benzofuran **89** from 1-bromo-2-iodobenzene and cyclohexanone. The α-arylation step to form the intermediate ketone **111**, in a reproduceable yield of 59%, was effected by the catalyst combination of $Pd_2(dba)_3$ with the ligand Xantphos, Cs_2CO_3 as the base at 80 °C in dioxane. The *O*-enolate cyclisation was performed in a more impressive yield of 95% employing a catalyst generated from $Pd_2(dba)_3$ with the ligand DPEphos, Cs_2CO_3 as the base at 100 °C in dioxane.



Scheme 3.21 Preparation of benzofuran **89**

Interestingly, the two activating ligands, Xantphos and DPEphos, although structurally very similar, propel independent catalytic cycles. The proposed catalytic cycle is illustrated in **Scheme 3.22**, highlighting the two distinct pathways.



Scheme 3.22 Proposed catalytic cycle

Xantphos: The proposed catalytic cycle depicts preliminary oxidative addition of the $Pd(0)L_n$ with the more labile arylhalide bond, in this case the Ar-I bond, to give the intermediate organopalladium(II) species **I**. Nucleophilic substitution of the iodide with the ketone enolate gives a second intermediate organopalladium(II) complex **II**.

Subsequent reductive elimination to form a new *C-C* bond gives the α-arylated ketone **111** with regeneration of the $Pd(0)L_n$ catalyst.

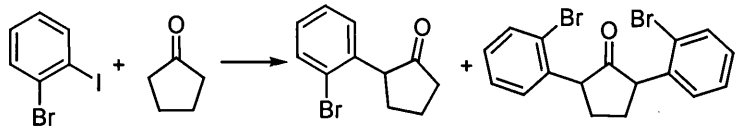
DPEphos: A second oxidative addition of $Pd(0)L_n$ with the remaining arylhalide bond, in this case the Ar-Br bond, provides the intermediate organopalladium(II) complex **III**. Enolisation of the ketone under base prior to its intramolcular nucleophilic displacement of the bromide gives the organopalladium intermediate **IV**. Finally, reductive elimination to form a new *C-O* bond gives the benzofuran **89** with regeneration of the $Pd(0)L_n$ catalyst.

In general, the rate-determining step for palladium catalysed *C-O* bond formations is the reductive elimination step and it is this step that is greatly influenced by ligand effects. Both Xantphos and DPEphos are both electron rich *bis*-phoshine ligands with a diaryl ether linkage and therefore have the ability to be *bis*-co-ordinating. Isolated Pd(Xantphos)RX complexes have shown that Xantphos has the ability to co-ordinate in either a *cis* or *trans* geometry with the bite angle increasing accordingly (*cf.* (*cis*) ~100° and (*trans*) ~150°).[111] Buchwald postulated that the unusually large bite angle of the (*trans*)-chelating Xantphos complex might be a result of the weak interaction of the oxygen atom with the palladium. The increased bite angles would aid reductive elimination.[112,113] Unfortunately, we cannot directly compare the two ligands as analogous studies of the DPEphos ligand have not be undertaken. However, the rigid *gem*-dimethyl backbone of the Xantphos ligand is the only structural anomaly between the two ligands and therefore must influence the reactivity. We postulate that free rotation around the DPEphos ether linkage is possible and therefore it is reasonable that the ligand can co-ordinate through either one or two of the phosphine groups. As a result, more than one ligand might co-ordinate to the palladium at any instance giving increased bulk and electron density to the palladium, increasing its ability to reductively eliminate and hence, encourage the formation of *C-O* bonds more effectively. The flexible nature of the ligand may also result in a more flexible bit angle, thus, improving the rate of reductive elimination.

3.5 Optimisation of palladium catalysed α-arylation

In order to evaluate the scope of the *O*-enolate cyclisation we first had to synthesise a range of α-arylated ketones. Although we decided to employ cyclohexanone as our case study for the optimisation of the *O*-enolate cyclisation, the conditions described for its α-arylation were, to a degree, non-transferable. The capricious nature of the reaction

was conveyed by the attempt to α-arylate cyclopentanone (**Table 3.4**). There are no examples in the literature which couple cyclopentanone but rather they opt for substituted adducts.[75,97,114] The increased ease of formation of multi-arylated products and aldol side products evidently had a negative effect on the outcome of the reaction.



119 **120**

Table 3.4 Optimisation of α-arylation of cyclopentanone[a]

Entry	Ligand	Base	Temp. (°C)	Conv. (%) (**119**:**120**)	Yield (%)
1	Xantphos	Cs_2CO_3	80	30 (1:0)	20
2	Xantphos	Cs_2CO_3	100	(1:2.5)	22
3	Xantphos	Cs_2CO_3	120	(1:3)	35
4	Xantphos	K_3PO_4	80	No reaction	0
5	Xantphos	NaO^tBu	80	Unknown mixture	0
6[b]	**5a**	Cs_2CO_3	80	Unknown mixture	0
7[b]	**3b**	Cs_2CO_3	80	Unknown mixture	0

Conditions: **a**: halide (1 eq.), ketone (1.2 eq.), $Pd_2(dba)_3$ (1 mol%), ligand (2.2 mol%), base (2.2 eq.), dioxane or toluene as solvent, 20 h; **b**: NaO^tBu (2.2 eq.), 0%.

Application of our optimised catalyst generated from $Pd_2(dba)_3$ and Xantphos with the weak base Cs_2CO_3 at 80 °C gave the desired α-arylated cyclopentanone **119** in a yield of 20% with no evidence of the diarylated ketone **120** (entry 1, **Table 3.4**). Although increasing the temperature improved the yield of the monoarylated product **119**, the product ratio increased in favour of the undesired diarylated product (entries 2 and 3). Employment of the weaker base, K_3PO_4, gave no reaction (entry 4) and employment of the stronger base, NaO^tBu, gave an unknown mixture of products, most likely as a result of the competing aldol reaction (entry 5). Moderate attempts to find an alternative ligand system failed (entries 6 and 7).

In an attempt to reduce the formation of the diarylated side product, alternative cyclopentanone derivatives were employed. First we attempted to α-arylate the cyclopentanone derivative **121** having been activated at the new tertiary α-carbon centre with an electron withdrawing ester group, which could be easily removed after coupling (**Table 3.5**). In theory, the tertiary carbon centre would be more easily deprotonated and additional stabilisation of the resulting carbanion by the ester group would increase the rate of arylation at that position. Unfortunately, the original catalyst generated from

$Pd_2(dba)_3$ and Xantphos with the weaker base Cs_2CO_3 did not give any new products and only starting materials were observed after 24 hours at elevated temperatures (entry 1, **Table 3.5**). Substituting the weaker base for the stronger NaHMDS or NaO^tBu bases gave only mixtures of products. Monitoring the reaction whilst increasing the temperature, employing a catalyst generated from $Pd_2(dba)_3$ and bulky, electron-rich ligand **3b** gave mixtures of products (entry 2). Employment of a catalyst generated from $Pd_2(dba)_3$ and Fu's $HP^tBu_3BF_4$ salt gave a new product by tlc analysis (entry 3), however, we were unable to isolate the product. The unsuccessful nature of this reaction may be attributed to the steric bulk of the tertiary carbon or perhaps an undesirable chelation between the ester group and the palladium centre.

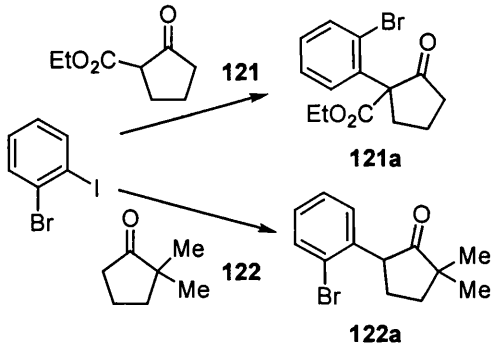


Table 3.5 Alternative cyclopentanone derivatives[a]

Entry	Ketone	Ligand	Base	Temp. (°C)	Conv. (%)	Yield (%)
1[b]	**121**	Xantphos	Cs_2CO_3	110	0	0
2[b]	**121**	**3b**	NaHMDS	80-100	Mixture	0
3	**121**	$HP^tBu_3BF_4$	NaO^tBu	50	73	0
4	**122**	Xantphos	Cs_2CO_3	80	0	0
5	**122**	Xantphos	NaO^tBu	100	23	-
6	**122**	$HP^tBu_3BF_4$	NaO^tBu	50-100	0	0
7	**122**	**3b**	NaO^tBu	50-100	0	0
8	**122**	Dave-phos	NaO^tBu	100	0	0
9	**122**	**5a**	NaO^tBu	50-80	24	12
10[c]	**122**	**5a**	K_3PO_4	50-80	0	0
11[b]	**122**	**5a**	NaO^tBu	100	54	-
12[b]	**122**	**5a**	NaO^tBu	110	67	50

Conditions: **a**: halide (1 eq.), ketone (1.2 eq.), $Pd_2(dba)_3$ (1 mol%), ligand (2.2 mol%), base (2.2 eq.), toluene; **b**: 1-bromo-2-chlorobenzene was employed as the halide precursor; **c**: $Pd(OAc)_2$ was employed as the Pd source.

We then turned our attention to the *gem*-dimethylcyclopentanone derivative **122**. Buchwald has previously shown an example of this ketone effectively coupling with

2,6-dimethyl-1-bromobenzene in the presence of a catalyst generated from $Pd(OAc)_2$ (0.5 mol%), ligand **5a** (1 mol%), NaO^tBu (1.3 eq.) as base, in toluene at 70 °C over 23 hours in a yield of 64%.[75] He detailed that the use of cyclopentanone under those conditions was unsuccessful as it was consumed too quickly in the competing aldol condensation. Completely blocking one of the α-carbons seems to have slowed down the aldolisation sufficiently for coupling to take place in preference. Again, our established conditions for cyclohexanone gave none of the desired product (entry 4) and employment of the stronger base NaO^tBu at an increased temperature of 100 °C gave only a 23% conversion (entry 5). No α-arylation was observed when alternative catalysts were applied that were generated from $Pd_2(dba)_3$ and ligands: $HP^tBu_3BF_4$, **3b** and Dave-phos **4a**, all of which are known to catalyse the α-arylation of ketones (entries 6-8). Employment of Buchwalds optimised conditions,[75] at the slightly higher temperature of 80 °C, gave the product in only 24% conversion (entry 9) and employment of a weaker base, K_3PO_4, gave starting materials only (entry 10). An increase in temperature gave a directly proportional increase in yield, although unknown side products began to form above 100 °C (entries 11-12). The optimised, although moderate, yield of 50% was attained employing $Pd_2(dba)_3$, ligand **5a** at 110 °C over 24 hours in toluene (entry 12).

We were also keen to expand the arylhalide scope in the reaction, introducing more sterically demanding and more highly substituted substrates. We chose to evaluate our cross-coupling conditions with commercially available 1,2-dihaloarenes, of which there are relatively few. **Table 3.6** shows some of the promising results obtained.

Our established Xantphos catalyst proved the most favourable for the cross-coupling of both 1-bromo-2-iodo-5-fluorobenzene and 1-bromo-2-iodo-4-fluorobenzene (entries 1 and 2, **Table 3.6**). Increasing both the catalyst loadings and temperature increased the yields of the desired α-arylated ketones. Surprisingly, significant amounts of the benzofuran product were observed employing 1-bromo-2-iodo-4-fluorobenzene in the presence of the catalyst generated from $Pd_2(dba)_3$ and Xantphos with Cs_2CO_3 at 110 °C (entry 2). Unsurprisingly, the attempted α-arylations of 1-bromo-2-iodo-3-bromobenzenes proved unsuccessful, producing mixtures of products (entries 3 and 4). Pleasingly, α-arylation of 1-bromo-2-chlorobenzene was successful providing an *ortho*-chloro substituent in order to compare reactivity of the cyclisation step (entry 5).

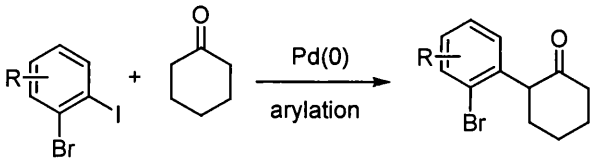
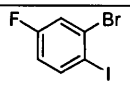
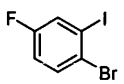
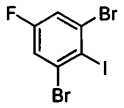
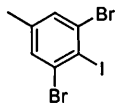
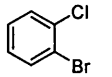


Table 3.6 Scope of halide source

Entry	Aryl halide	Xantphos (conv. %)	DPEphos (conv. %)
1[a, b, c, d]		35	15
2[a, b, c, d]		49 +50 benzofuran	12
3[a, e, f, g]		0	0
4[a, e, f, g]		0	0
5[f]		62	-

Conditions: **a**: $Pd_2(dba)_3$ (1.0 mol%), ligand (2.2 mol%), Cs_2CO_3 (2.2 eq.), dioxane, 80 °C, 24 h; **b**: $Pd_2(dba)_3$ (2.0 mol%), ligand (4.5 mol%), Cs_2CO_3 (2.2 eq.), dioxane, 100 °C, 24 h; **c**: $Pd_2(dba)_3$ (2.5 mol%), ligand (6.0 mol%), Cs_2CO_3 (2.2 eq.), toluene, 110 °C, 22 h; **d**: $Pd_2(dba)_3$ (2.5 mol%), ligand (6.0 mol%), NaHMDS (2.2 eq.), toluene, 110 °C, 22 h; **e**: alternative ligands have been employed but to no avail: (*rac*)-BINAP, **1a**, **3a**, **6a**, **6b**, **6c**; **f**: NaHMDS with Xantphos gave the aldol product; **g**: 5 mmol scale; $Pd_2(dba)_3$ (2.0 mol%), Xantphos (4.5 mol%), 100 °C .

3.6 Novel palladium-catalysed *O*-enolate cyclisation

After numerous experiments we had successfully α-arylated a range of ketones. **Table 3.7** charts the scope of both the α-arylation coupling and *O*-enolate cyclisation. The *O*-enolate cyclisation was found to be effected by the same catalyst system [$Pd_2(dba)_3$, DPEphos] although some variation in the choice of base was necessary.

Simple cyclic ketones were tolerated well in both reactions when coupled to 1-bromo-2-iodobenzene (entries 1, 2 and 5). Unfortunately, our attempts to cyclise α-arylated cyclopentanone **119** and a *gem*-dimethyl derivative **125** failed (entry 3 and 4; see section **3.8**). The successful α-arylation of cyclohexanone with 1-bromo-2-chlorobenzene gave a chloro-substituted arene-ring which proved an effective substrate for the cyclisation although the stronger base, NaHMDS was required (entry 2). Simple aryl- and ketal-substituted ketones were also tolerated well in combination with NaO^tBu as base (entry 7 and 13 respectively).

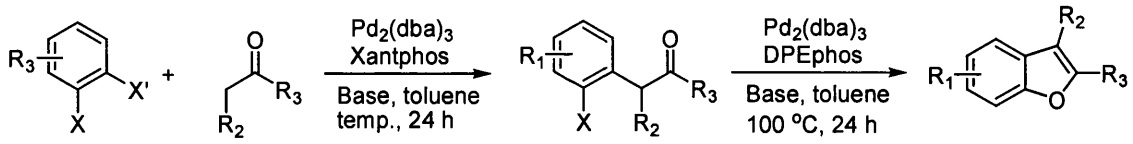
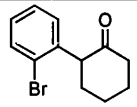
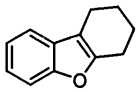
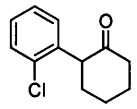
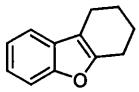
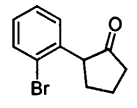
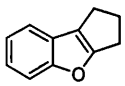
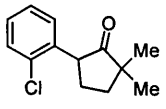
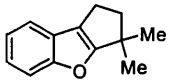
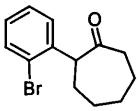
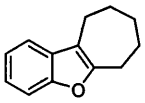
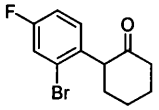
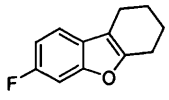
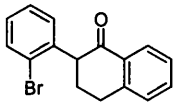
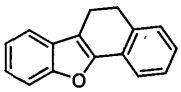
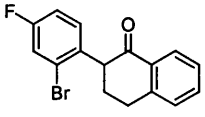
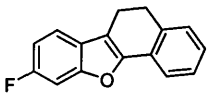
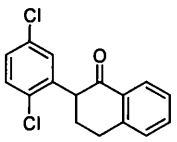
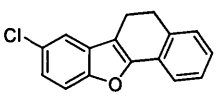
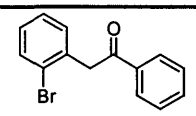
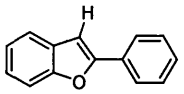
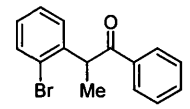
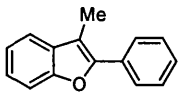
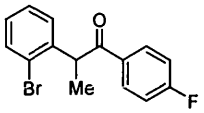
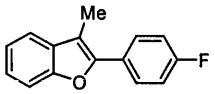
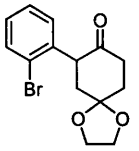
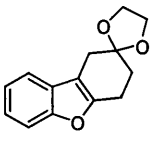
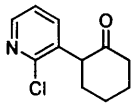
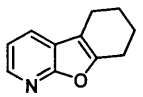
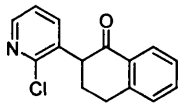
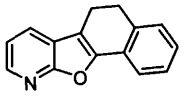


Table 3.7 Scope of palladium catalysed α-arylation and *O*-enolate cyclisation

Entry	Ketone	Base	Yield[a] (%)	Benzofuran	Base	Conv. (%)	Yield[b] (%)
1[c]	 **111**	Cs_2CO_3	58	 **89**	Cs_2CO_3	100	95
2[c]	 **123**	Cs_2CO_3	59	 **89**	Cs_2CO_3 NaHMDS	100 100	16 94
3[d]	 **119**	Cs_2CO_3	35	 **124**		0	0
4	 **125**	Cs_2CO_3	50	 **126**		0	0
5	 **127**	NaHMDS	62	 **128**	NaHMDS	100	95
6	 **129**	Cs_2CO_3	39	 **130**	NaO^tBu Cs_2CO_3	81 70	71 63
7	 **131**	NaO^tBu	52	 **132**	NaO^tBu		81
8	 **133**	NaO^tBu Cs_2CO_3	64 57	 **134**	NaO^tBu	74	64
9[e]	 **135**	NaO^tBu	67	 **136**		0	0

10[f]	 137	NaO^tBu	51	 138	Cs_2CO_3	50	-
11[f]	 139	NaO^tBu	71	 140	NaO^tBu	80	70
12[f]	 141	NaO^tBu	60	 142	NaO^tBu	68	48
13[c]	 143	Cs_2CO_3	58	 144	NaO^tBu	73	63
14[c]	 145	Cs_2CO_3	35	 146	NaO^tBu	86	45
15	 147	NaO^tBu Cs_2CO_3	0 0	 148	NaO^tBu	100	83

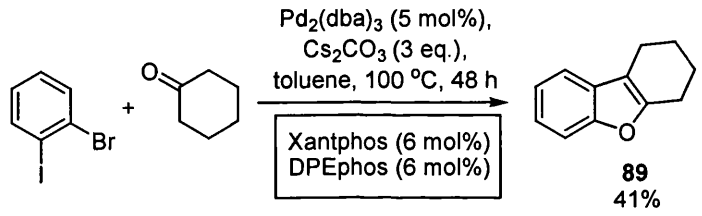
Conditions: **a**: Halide (1 eq.), ketone (1.2 eq.), $Pd_2(dba)_3$ (0.5 mol%), Xantphos (1.2 mol%), base (1.5 eq.), toluene, 110 °C, 24 h; **b**: α-arylated ketone (1 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6 mol%), base (1.5 eq.), dioxane, 100 °C, 24 h; **c**: 100 °C; **d**: 120 °C; **e**: bases employed: Cs_2CO_3, NaO^tBu, NaHMDS; ligands employed: DPEphos, Xantphos, **3b**, **5a**, Dave-phos **4a**; **f**: ligand: $HP^tBu_3BF_4$ (1.2 mol%), 60 °C.

The α-arylation of acyclic substrates was best afforded employing a catalyst generated from $Pd_2(dba)_3$ and the salt $HP^tBu_3BF_4$ in the presence of a strong base NaO^tBu at lower temperatures of 60 °C (entries 10-12). Acyclic substrates also performed well under the cyclisation conditions although the acetophenone derivative (entry 10) gave lower conversions than the propiophenone examples (entries 11 and 12). Substitution on the aryl portion was also achieved with the incorporation of mono-fluoro and pyridyl units (entries 6, 8, 14 and 15). Unfortunately, for reasons not fully understood, cyclisation of the α-tetralone enolate with an activated aryl chloride did not proceed (entry 9). Several attempts employing a range of bases (Cs_2CO_3, NaO^tBu, NaHMDS) and ligands (DPEphos, Xantphos, **3b**, **5a**, Dave-phos) were ineffective. When cyclohexanone was coupled to 2-chloro-3-bromopyridine significant amounts of the cyclised product was obtained (entry 14). Unfortunately, the presence of a heteroatom *ortho* to an Ar-X bond increases the lability of the Ar-X bond and makes it more susceptible to nucleophilic

attack (S_NAr). When the isolated α-arylated ketone was reacted with base only, it took twice as long to achieve complete conversion to the cyclised product. When we attempted the same reaction employing α-tetralone none of the intermediate ketone was isolated as the rate of cyclisation was even faster, despite lowering the temperature (entry 15).

3.6.1 One-pot Strategy

Scheme 3.23 illustrates the potential for a tandem one-pot reaction employing one catalyst-system for both reaction cycles. Our initial quest to find a single ligand to effectively catalyse both steps of the reaction was unsuccessful, however, a one-pot synthesis was achieved when both ligands were employed simultaneously. Optimised conditions employed 5 mol% $Pd_2(dba)_3$, with 6 mol% of each ligand and an increased reaction time of 48 hours.

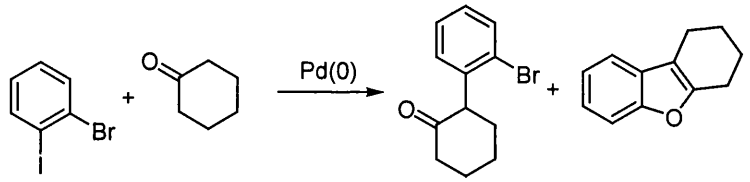


Scheme 3.23 One-pot two-ligand approach

A second ligand screen was carried out on the advent of new, commercially available subclasses of ligands with several catalyst systems showing potential (**Table 3.8**). Unfortunately, most of the reaction mixtures were obscured by degradation or aldol products. The ligand screen was carried out employing the general catalyst system $Pd_2(dba)_3$ with the ligand of choice in the presence of the weak base Cs_2CO_3 in toluene so that a direct comparison to the established one-pot two-ligand approach could be made.

Application of the bulky, monodentate binaphthyl-P^{t}Bu$_2$ ligand **1a** gave only an 11% conversion to the arylated ketone **111** with none of the benzofuran **89** being observed (entry 1, **Table 3.8**). We hoped to aid the reductive elimination step of the cycle by replacing the monodentate BINAP ligand with the bidentate version (*rac*)-BINAP, however, this lowered the yield of the arylated ketone somewhat (entry 2). The presence of the *tert*-butyl group may be of importance, however, employment of a biaryl P^{t}Bu$_2$ analogue **3b** gave disappointing results (entry 3). Employment of the dicyclohexylphosphino ligand Dave-phos, **4a** gave a more encouraging result,

producing 9% of the arylated ketone although still none of the benzofuran product was evident (entry 4). Anthracene based ligands **6a** and **6b** revealed a similar trend, with the dicyclohexylphosphine ligand performing most effectively (entries 5 and 6).



111 **89**

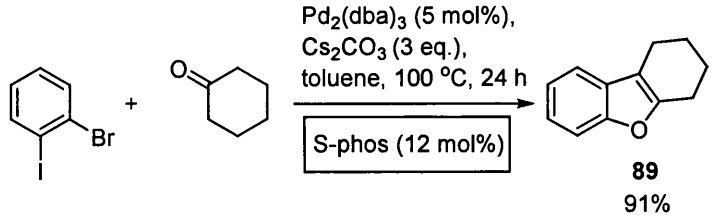
Table 3.8 Ligand screen[a]

Entry	Ligand	Arylated ketone **111** (conv. %)	Benzofuran **89** (conv. %)	Starting Materials and Products[d]
1	**1b**	11	0	halide + ketone
2	(*rac*)-BINAP	Negligible	0	halide + 20% ketone + degradation
3	**3b**	Negligible	0	halide + 10% ketone + degradation
4	Dave-phos, **4a**	9	0	halide + degradation
5	**6a**	9	0	halide + degradation
6	**6b**	Negligible	0	halide + degradation
7	**12a**	0	0	halide + ketone + 10% degradation
8	**12b**	9	7	halide + degradation
9[b]	**12b**	25	25	halide + ketone
10	**12c**	0	0	halide + 5% ketone + degradation
11	X-phos	Negligible	9	halide + degradation
12	^{t}Bu-X-phos	Negligible	0	halide + degradation
13	S-phos	9	20	halide + degradation
14[b]	S-phos	Negligible	95	degradation
15[c]	S-phos	0	100	0

Conditions: **a**: 1-bromo-2-iodobenzene (1 eq.), cyclohexanone (1.2 eq.), $Pd_2(dba)_3$ (2.5 mol%), ligand (6 mol%), Cs_2CO_3 (1.5 eq.), toluene, 80 °C, 24 h; **b**: $Pd_2(dba)_3$ (5 mol%), ligand (6 mol%), Cs_2CO_3 (3 eq.) toluene, 100 °C, 40 h; **c**: $Pd_2(dba)_3$ (5 mol%), ligand (12 mol%), Cs_2CO_3 (3 eq.), toluene, 100 °C, 24 h; **d**: NMR conversions (*cf.* halide).

Recently, ferrocene based ligands have appeared in the literature with more frequency and have shown success in a number of palladium-catalysed *C-O* bond forming reactions.[115] Unfortunately, application of the *bis*-chelating variations with isopropyl **12a** and phenylphosphino groups **12c** gave none of the desired products (entry 7 and 10). Pleasingly, the *tert*-butyl analogue catalysed both steps in the reaction sequence producing 9% of the arylated ketone and 7% of the benzofuran (entry 8). The respective yields increased to 25% when the catalyst loading was increased to 5 mol% Pd and 6 mol% ligand (entry 9). More highly substituted biaryl ligands were also made

commercially available and showed the most promise in our system. Although the bulky dicyclohexylphosphine ligand X-phos gave poor yields of the benzofuran product it gave complete cyclisation of the arylated ketone (entry 11). Again the *tert*-butyl analogue showed inadequate reactivity in comparison (entry 12). Switching to the novel 2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl ligand, S-phos, provided the arylated ketone in 9% with 20% conversion to the benzofuran product (entry 13). Almost complete conversion was attained on increasing the catalyst loading to 5 mol% Pd and 6 mol% ligand (entry 14). Finally, complete conversion was attained employing excess ligand: 5 mol% Pd and 12 mol% ligand (entry 15, **Table 3.8**; **Scheme 3.24**). Ultimately, a one-pot one-ligand approach has been realised (**Scheme 3.24**).



Scheme 3.24 Novel tandem palladium-catalysed benzofuran synthesis

Table 3.9 charts the scope of the palladium catalysed one-pot one-ligand synthesis of the benzofuran motif. The same catalyst system [$Pd_2(dba)_3$, S-phos] was applied to all of the substrates although a change in base from Cs_2CO_3 to NaO^tBu was found to be beneficial in certain cases.

Entry 1 exemplifies the one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*β*]furan **89** from cyclohexanone and 1-bromo-2-iodobenzene which proceeded in almost quantitative yield. The overall two-step yield was considerably lower giving only 55% of the benzofuran, firmly establishing the one-pot protocol as a competitive alternative to the two-step approach. The equivalent aryl chloride reaction gave a disappointing 27% of the cyclised product, however, 68% of the arylated ketone was isolated, giving a combined yield of 95% suggesting that the rate of reaction was slower in comparison to the aryl bromide substrate (entry 2). Again, the catalyst system was unable to execute cyclisation of the arylated cyclopentanone substrate (entry 3: see section **3.8**). Insufficient yields were attained for the one-pot cross-coupling reaction between α-tetralone and 1-bromo-2-iodobenzene, however, the previously elusive chloro-substituted analogue gave the desired benzofuran, albeit in a yield of only 17% (entries 4 and 5: *cf.* entry 9, **Table 3.7**).

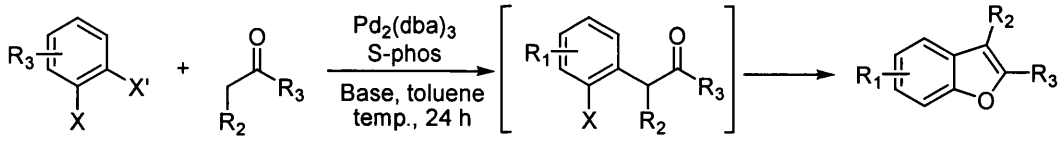
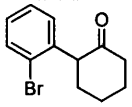
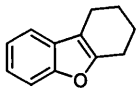
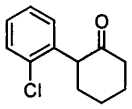
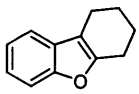
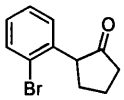
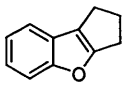
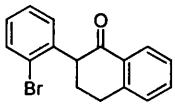
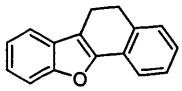
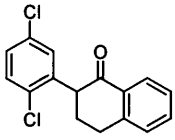
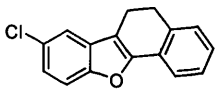
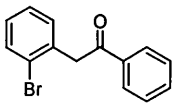
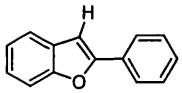
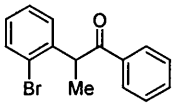
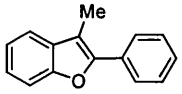
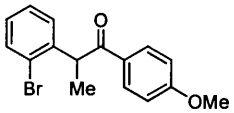
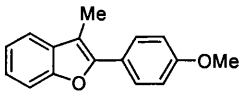


Table 3.9 Scope of One-pot Benzofuran synthesis[a]

Entry	Ketone	Yield (One-pot) (%)	Benzofuran	Base	Yield (One-pot) (%)	Yield[b] (Two-pot) (%)
1	 **111**	0	 **89**	Cs_2CO_3	91	55
2	 **122**	68	 **89**	Cs_2CO_3	27	56
3[c]	 **119**	38	 **124**	Cs_2CO_3	0	0
4	 **131**	14	 **132**	NaO^{t}Bu	20	42
5	 **135**	23	 **136**	NaO^{t}Bu	17	0
6	 **137**	74	 **138**	NaO^{t}Bu	23	26
7	 **139**	81	 **140**	NaO^{t}Bu	19	50
8[d]	 **150**	64	 **151**	NaO^{t}Bu	36	Unknown (for –F **142** 29%)

Conditions: **a**: halide (1 eq.), ketone (1.5 eq.), $Pd_2(dba)_3$ (5 mol%), ligand (12 mol%), base (3 eq.), toluene, 100 °C, 24 h; **b**: overall yields from **Table 3.7**; **c**: 80 °C, at 100 °C 19% conv. to arylated; **d**: resubjecting the arylated ketone to the catalyst system provided the benzofuran in 67% yield.

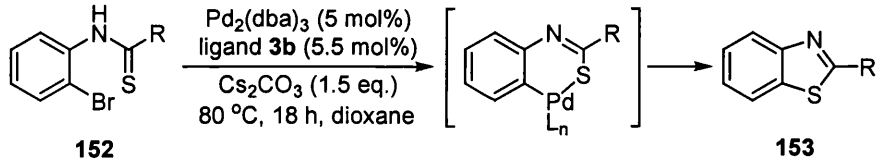
Conversely, acyclic ketones proved very effective with both arylated and cyclised products being isolated in complete mass balance (entries 6-8). Both the one and two-step protocols gave comparable yields of the cyclised product for the example employing acetophenone (entry 6). The poor conversion from arylated ketone to cyclised benzofuran may be attributed to deterioration of catalyst activity over time. When isolated arylated *p*-methoxypropiophenone was reacted with newly generated catalyst over a shorter period of 12 hours, 67% of the desired benzofuran was obtained (entry 8). This demonstrates the effectiveness of the catalyst and supports the concern regarding the catalyst longevity.

In general, the two-pot protocol gives more consistent results and is complimented by the one-pot protocol.

3.7 Thio-ketones to Benzothiophenes

Palladium catalysed *C-S* bond formations are known but they are much less common than the corresponding *C-O* or *C-N* bond forming reactions. We were interested in whether the concept of intramolecular *O*-enolate arylation could be extended to thio-ketone *S*-enolate **154** arylation to give a new route to benzothiophenes **155** (**Scheme 3.26**).

One representative example reported in the literature by the group of Castillon outlines an intramolecular palladium catalysed study employing nucleophilic thiocarbonyl moieties for the synthesis of 2-substituted-benzothiazoles **153** (**Scheme 3.25**).[116]



152
R= Me, Ph, ^{t}Bu, adamantyl

153
68-100%

Scheme 3.25 Intramolecular cyclisation of *o*-bromoarylthioamides

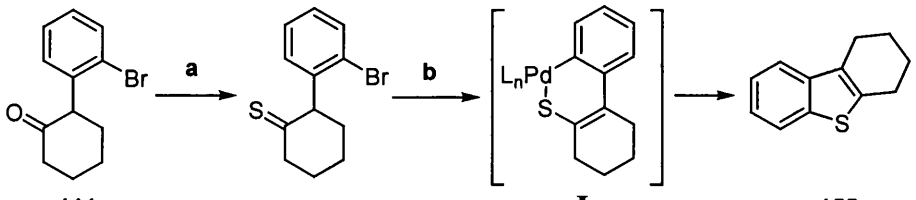
The *o*-bromoarylthioamides **152** were prepared from the corresponding amides by treatment with Lawesson's reagent in excellent yields (>87%). They found that the cyclisation was achieved in the presence of a weak base (Cs_2CO_3) and a catalyst generated from the bulky monodentate *tert*-butyl phosphine ligand **3b** and $Pd_2(dba)_3$. The order of reaction is unclear; whether or not the thiocarbonyl chelates to the palladium centre prior to deprotonation or if deprotonation occurs to give the more

nucleophilic thio-amidate with subsequent attack at the palladium centre. The same argument may be applied to our system.

3.7.1 Novel palladium-catalysed *S*-enolate cyclisation

First, we had to prepare a range of α-arylated thio-ketones from the corresponding α-arylated ketones. The preparation of thio-ketones has received continued interest since the earliest method reported separately back in 1869 by Henry[117] and by Wislicenus[118] employing phosphorus pentasulfide.[119] Development of additive combinations and the adoption of new sulfonating agents; Lawesson's reagent,[120] Davy's reagent and analogues thereof,[121] use of *bis*(trimethylsilyl)sulfide in combination with trimethylsilyltriflate[122] and more recently, phosphorus pentasulfide adsorbed onto activated basic alumina,[123] has brought this reaction into the mainstream. These methods have also been applied to the formation of thio-aldehydes,[124] thio-esters,[125] thio-amides and cyclic variants thereof.[125-128]

Our original α-arylated cyclohexanone **111** was easily converted to the corresponding thio-ketone **154** by treatment with phosphorus pentasulfide in combination with hexamethyldisiloxane (**Scheme 3.26**).[125,129-131]



111 **154** 71% **I** **155** 74%

Conditions: **a**: Ketone **111** (1.0 eq.), P_4S_{10} (0.3 eq.), $(TMS)_2O$ (1.7 eq.), toluene, 90 °C, 21 h; **b**: thio-ketone **154** (1.0 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6.0 mol%), Cs_2CO_3 (1.5 eq.), toluene, 100 °C, 20 h.

Scheme 3.26 Novel palladium-catalysed *S*-enolate cyclisation

Pleasingly, cyclisation is achieved employing identical conditions used for the parent ketone cyclisation to give the expected benzothiophene **155** in an excellent yield of 74% possibly *via* the organopalladium intermediate **I**. Application of this strategy to representative α-arylated ketones provided a range of 2,3-disubstituted benzothiophenes, illustrating the utility of the reaction (**Table 3.10**).

The thio-ketones were prepared in the same manner employing phosphorus pentasulfide in combination with hexamethyldisiloxane. Multiple filtration steps to remove the residual phosphorus pentasulfide resulted in lower yields of the thio-ketone being

attained. New methods employing phosphorus pentasulfide adsorbed onto basic alumina would aid recovery.[123]

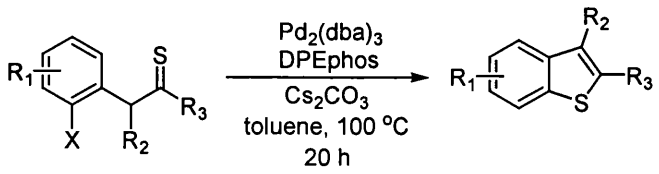
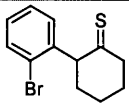
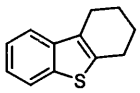
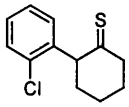
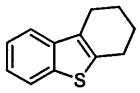
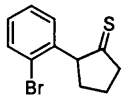
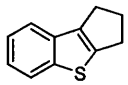
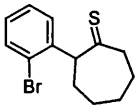
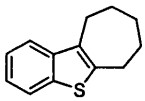
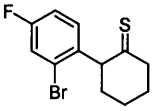
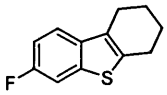
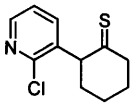
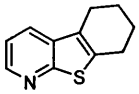


Table 3.10 Scope of benzothiophene synthesis

Entry	Thio-Ketone[a]	Yield (%)	Benzothiophene[b]	Yield (%)
1	 **154**	71	 **155**	74
2	 **156**	40	 **155**	53
3	 **157**	38	 **158**	44
4	 **159**	40	 **160**	52
5	 **161**	53	 **162**	57
6[c]	 **163**	0	 **164**	57

Conditions: **a**: ketone (1 eq.), P_4S_{10} (0.3 eq.), $(TMS)_2O$ (1.7 eq.), toluene, 90 °C, 21 h; **b**: halide (1 eq.), ketone (1.2 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6 mol%), Cs_2CO_3 (1.5 eq.), toluene, 100 °C, 24 h; **c**: direct cyclisation of thio-ketone upon formation.

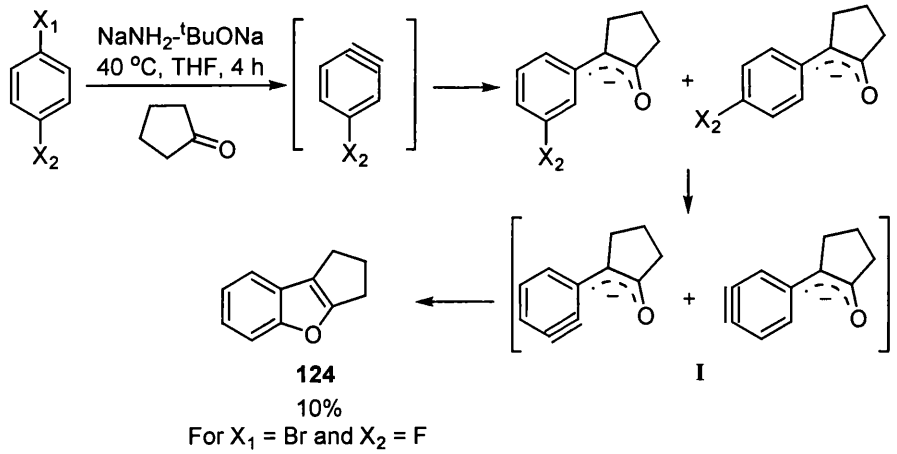
Simple cyclic thio-ketones were cyclised effectively with both aryl bromide **154** and aryl chloride **156** substrates (entries 1-4, **Table 3.10**). A slightly lower yield was obtained with the chloro-substrate **156**, perhaps as a result of the slower rate of oxidative addition of the palladium to the *Ar-Cl* bond and therefore reduced reactivity of the catalyst in the presence of the nucleophilic sulfur. Pleasingly, the cyclopentanethione substrate **157** cyclised to give the corresponding benzothiophene

158 in a moderate yield of 44% (entry 3; see section **3.8**). Entry 5, incorporating a mono-fluoro unit, demonstrates that substituents on the aryl ring can be tolerated. Unfortunately, attempts to prepare the pyridyl-thioketone substrate **163** failed, providing the corresponding benzothiophene **164** directly *via* a non-palladium catalysed pathway (entry 6). The S_NAr cyclisation was realised as a result of the increased nucleophilicity of the sulfur enolate (*cf. O*-enolate, **Table 3.7**).

3.8 Cyclisation of α-arylated cyclopentanone

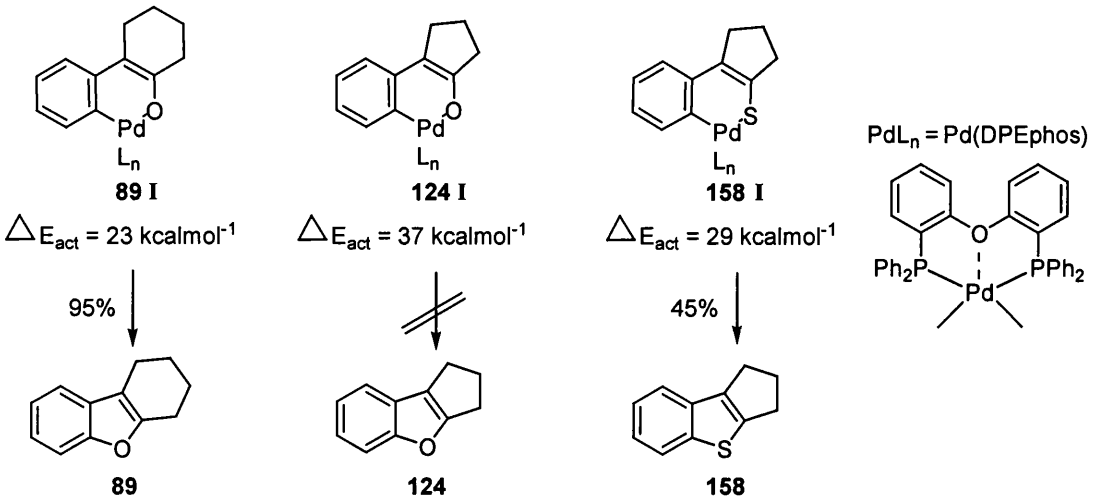
Our attempts to cyclise α-arylated cyclopentanone **119** have failed. The α-arylated cyclohexanone **111** cyclises in up to 95% yield and the analogous thio-ketone derivative **157** cyclises to form a new *C-S* bond in a reasonable yield of 44%. We carried out simple computational calculations to determine whether or not the theoretical intermediate transition states differ greatly enough to account for this observation.

The unsubstituted cyclopentanone benzofuran **124** has been synthesised previously by Caubere *et al. via* an aryne S_NAr approach, although in very low yield (**Scheme 3.27**).[132] Caubere discovered that by adding a dihalobenzene to an already stirred solution of a ketone and the complex base $NaNH_2$-^{t}BuONa in THF under an inert atmosphere at a moderate 40 °C the corresponding benzofuran was formed, presumably *via* an intermediate aryne condensation reaction. They found that the best results were obtained with 1,4-disubstituted benzenes. The benzyne intermediates **I** appear less sterically strained or encumbered than our corresponding palladium complex (**124I**, **Scheme 3.28**) and, as a result, the formation of the desired benzofuran **124** seems more feasible.



Scheme 3.27 Condensation of cyclopentanone enolate with 1,4-substituted benzenes

The intermediate palladium complexes of the aforementioned α-arylated ketones are depicted in **Scheme 3.28**. All calculations were carried out by Inaki Morao, Pfizer, employing a Spartan02 package and the geometries optimised using the semi-empirical approach PM3™ (see **Appendix 1**).

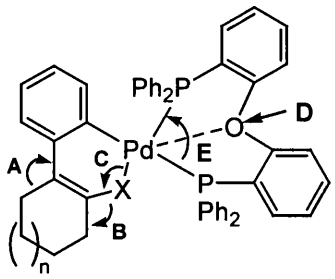


Scheme 3.28 Comparison of activation energies of palladium complexes

The observed experimental results can be explained simply by the calculated activation energies, assuming that the *C-O* or *C-S* bond forming step is in fact the rate-determining step (see Introduction, **Chapter 1**). The activation barrier for the α-arylated cyclohexanone TS **89I** is relatively low (23 kcalmol^{-1}) and therefore gives the desired cyclised product **89** in excellent yield. However, the activation barrier for the α-arylated cyclopentanone TS **124I** is significantly higher (37 kcalmol^{-1}) as a result of a more geometrically strained transition state, rendering cyclisation unlikely. Unsurprisingly, the calculated activation barrier for the α-arylated cyclopentanethione **158I** is intermediate in value (29 kcalmol^{-1}), exemplified by the moderate conversion obtained experimentally.

A more significant shift in exocyclic bond angle sizes (**A** and **B**) was calculated for the cyclopentanone versus the cyclohexanone transition state (**124I** vs **89I**) upon its formation from the starting materials (**Figure 3.2**). This shift imposes more strain in the structure, increasing the energy of activation accordingly. The distance, **D** between the palladium centre and the oxygen of the DPEphos ligand increased by the same magnitude in each case, decreasing the bite angle of the ligand, **E**. This would decrease its effectiveness in the reductive elimination step of the cycle. However, this distance, **D** remains the same in the otherwise identical sulfur TS **158I**, unaltering the bite angle, **E** which may explain why this reaction proceeds to a certain extent. The significantly

longer *C-S* bond length (*C-S* 1.76 *cf. C-O* 1.33) and increased nucleophilicity of the sulfur compared to oxygen may also contribute to its success.



X	n	A	B	C	D	E
O	1	118-125	116-121	136-149	2.16-3.61	160-106
O	0	124-136	124-130	132-147	2.36-3.61	168-106
S	0	125-132	121-130	106-111	3.66-3.63	105-106

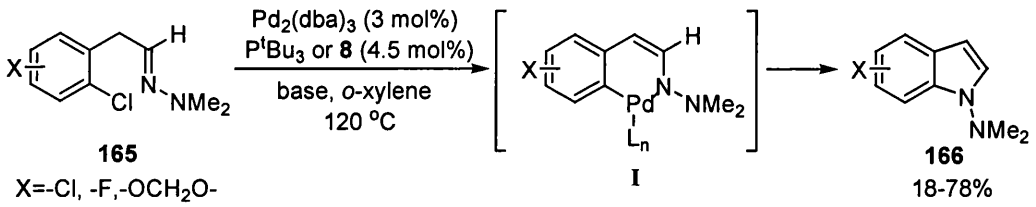
Values given correspond to starting material and complex respectively

Figure 3.2 Calculated bond angles and distances

3.9 Indole Strategy

The indole ring system is of great importance as many derivatives exhibit pharmacological and physiological activity and as a consequence, many methods exist for its formation.[133] In the past decade there has been a particular emphasis on palladium-catalysed strategies with the exponential explosion of new catalysts for palladium catalysed *C-N* bond formations. One of the most useful methods involves the palladium catalysed coupling of *o*-haloaniline precursors to form indoles. We were interested in whether the concept of intramolecular *O*-enolate arylation could be extended to imino-*N*-enolate **167** arylation to give a new route to indoles (**Scheme 3.30**).

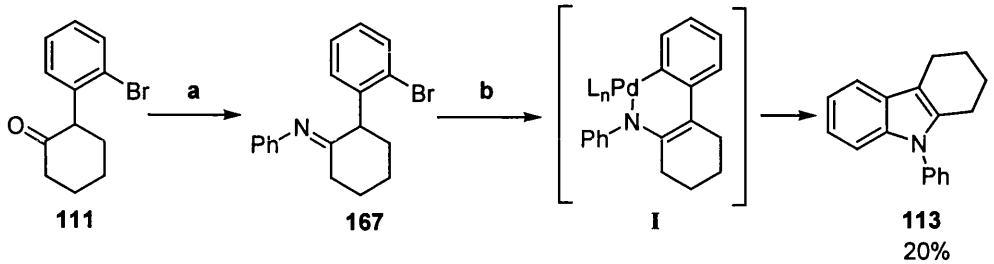
In 2000, Watanabe *et al.* described a reaction of particular interest involving the palladium-catalysed intramolecular cyclisation of *o*-chloroarylacetaldehyde *N,N*-disubstituted hydrazones **165** to give 1-aminoindole derivatives **166** *via* a plausible aryl(enamido)palladium complex **I** (**Scheme 3.29**).[134] They formed the enamido-palladium complex **I** *in-situ* in the presence of a weak base (Rb_2CO_3 or Cs_2CO_3) and a catalyst generated from $Pd(dba)_2$ and a bulky, electron-rich phosphane ligand $P^t(Bu)_3$ or 2-(dimethylaminomethyl)-1-(di-*tert*-butylphosphanyl)ferrocene **8**, to give the desired indole products.



Scheme 3.29 Intramolecular palladium-catalysed '*N*-enolate' cyclisation

3.9.1 Novel palladium catalysed *N*-enolate cyclisation

Our strategy involves the initial formation of an imine (*cf.* hydrazone **165**) by direct heating of the ketone **111** and aniline at 110 °C in toluene employing molecular sieves to remove the water generated. Consecutive palladium-catalysed cyclisation of the imine to give *N*-phenylindole *via* the postulated aryl(enamido)palladium complex **I** similar to the intermediate described by Watanabe in **Scheme 3.29** (**Scheme 3.30**).

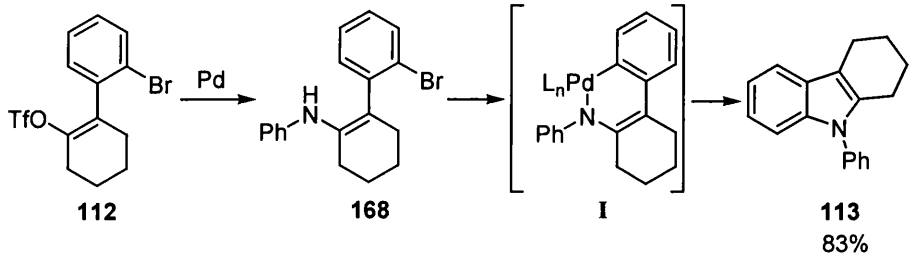


111 **167** **I** **113** 20%

Conditions: **a**: ketone **111** (1.0 eq.), aniline (1.1 eq.), 4Å MS, toluene, 110 °C, 18 h; **b**: imine (1.0 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6.0 mol%), Cs_2CO_3 (1.5 eq.), toluene, 100 °C, 24 h.

Scheme 3.30 Novel palladium-catalysed *N*-enolate cyclisation

This methodology compliments the methodology previously reported from within our group by Willis and Brace describing a tandem palladium catalysed alkenyl and aryl *C-N* bond forming reaction to form the indole motif (**Scheme 3.31**). Application of the catalyst system [Pd_2dba_3 and DPEphos], later adopted for our synthesis of the benzofuran motif, resulted in formation of indoles in excellent yield. They discovered that the first palladium coupling occurs intermolecularly between the vinyl triflate and the aniline with subsequent intramolecular cyclisation between the newly formed enamide **168** and the arylbromide functionality to give the resulting indole **113**. It is realistic to believe that the cyclisation step is achieved *via* a similar transition state to the one depicted in **Scheme 3.31** which is identical to the transition state proposed for our imine cyclisation (**Scheme 3.30**).



112 **168** **I** **113** 83%

Conditions: Pd: aniline, $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6.0 mol%), Cs_2CO_3 (2.2 eq.), toluene, 100 °C.

Scheme 3.31 Palladium-catalysed enamide cyclisation

Unsurprisingly, application of the catalyst generated from $Pd_2(dba)_3$ and DPEphos to our imine system successfully effected the intramolecular cyclisation of the imine, albeit

in low yield. Despite crude NMR analysis confirming quantitative formation of the imine, after palladium catalysis there was unreacted aniline present in the reaction mixture. The apparent instability of the imine to the reaction conditions is an issue that must be addressed. Nevertheless, the preliminary studies have shown promise and further studies to establish an optimal catalyst system will be undertaken within the Willis laboratory.

3.10 Concluding Observations

We have shown that we can successfully prepare substituted benzo[*β*]furans *via* a novel intramolecular *O*-enolate cyclisation of α-arylated ketones, exploiting a powerful combination of ligand and palladium source [$Pd_2(dba)_3$ and DPEphos]. The reaction conditions are general and can be used to obtain a wide range of substituted rings in excellent yields. A one-pot protocol employing a catalyst generated from $Pd_2(dba)_3$ and S-phos compliments the established two-pot approach. The same catalyst system [$Pd_2(dba)_3$ and DPEphos] is also effective for thio-ketone substrates, providing the corresponding benzo[*b*]thiophenes in good yield. A single example of the application of our methodology towards the synthesis of the indole motif has shown promise and further work in this area will be undertaken within the Willis laboratory.

Since the publication of our results, Chen and Dormer have published a CuI-catalysed method employing similar α-arylated ketones to form substituted benzofurans.[135] They found that the cyclisation occurred employing CuI (10 mol%), a mild base (K_2CO_3), in DMF overnight, although elevated temperatures of 105 °C were required to give excellent yields. This investigation complements our findings.

3.11 References

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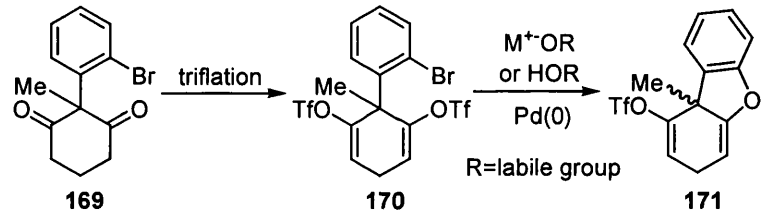
Chapter 4 Palladium Catalysed Alkenyl- and Aryl-*C-O* Bond Formations: A Cascade *O*-Annulation Route to the Benzofuran Motif

The recent report from the Willis laboratory by Brace outlined a tandem palladium-catalysed *N*-alkenylation/arylation of primary amines to form indole (**Chapter 3, Scheme 3.31**).[1] Herein we report our investigation towards an equivalent tandem palladium catalysed *O*-alkenylation/arylation as a complimentary protocol towards the formation of the benzofuran motif.

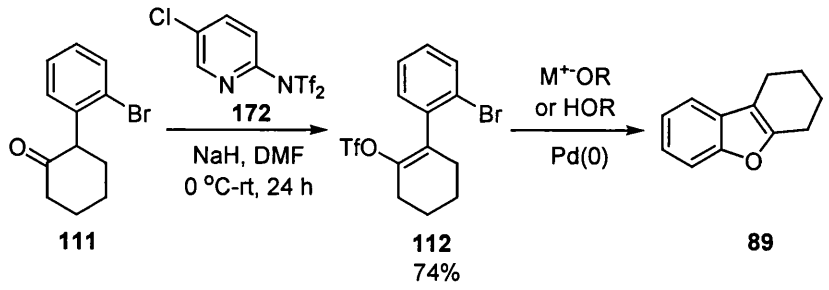
4.1 Proposed methodology: Tandem palladium catalysed *C-O* bond formations exploiting an oxygen surrogate

We envisaged that diketone **169** could be effectively transformed into the symmetrical *bis*-vinyl triflate **170** under standard triflation conditions.[2-4] We had proposed that desymmetrisation of **170** in the presence of a palladium catalyst invoking an unprecedented double insertion of an oxygen surrogate would give the aryl enol ether **171** (**Scheme 4.1**).[5]



Scheme 4.1 Proposed desymmetrisation methodology

Preliminary results were carried out using the more simplified α-arylated cyclohexanone **111** which has been readily transformed into the corresponding triflate **112** by treatment with triflamide **172** and the strong base, NaH at 0 °C in a reproducible yield of 74% (**Scheme 4.2**). The envisaged transformation of the triflate **112** coupling with an oxygen surrogate in the presence of a palladium catalyst gave the expected 1,2,3,4-tetrahydrobenzofuran **89**. The results will be discussed in this chapter.



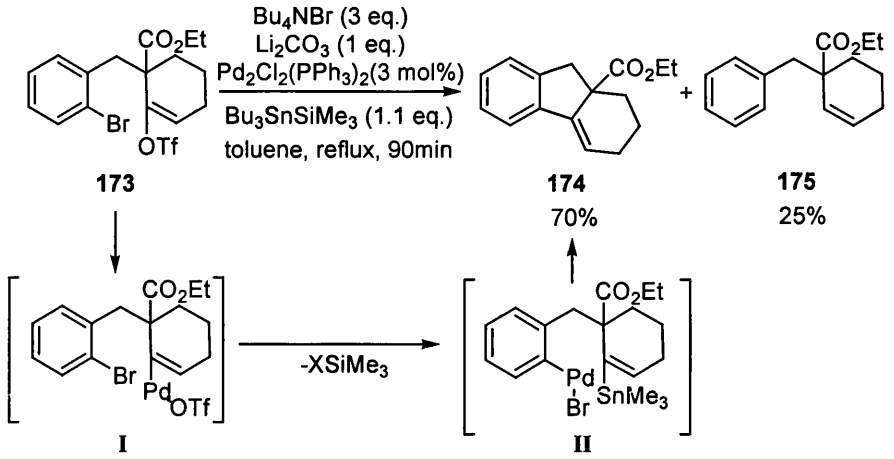
Scheme 4.2 Proposed tandem *C-O* bond formation towards synthesis of benzofurans

4.1.1 Established palladium catalysed tandem one-pot protocols

There are several reports in the literature that describe one-pot tandem palladium-catalysed reactions where one catalyst system successfully executes more than one *C-C*, *C-X* or *C-M* bond formation in sequence. There are far fewer reports that describe palladium-catalysed tandem *C-N* bond formations involving double insertion reactions of nucleophilic amines and, to the best of our knowledge, there are no examples of double *C-O* bond formations employing masked hydroxyl nucleophiles. Relevant representative examples of one-pot protocols for the formation of *C-C* and *C-N* bonds are described.

Tandem *C-M/C-C* bond formations

In 1991, Shibasaki *et al.* described a tandem transmetalation-intramolecular cyclisation to successfully construct a novel *C-C* bond bridging an aryl halide and a proximal vinyl triflate, employing $R_3SnSiMe_3$ in a chemoselective manner (**Scheme 4.3**). The starting triflate **173** was prepared from the condensation product of ethyl 2-oxocyclohexanecarboxylate and *o*-bromobenzyl bromide by treatment with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine as base. The determined optimal conditions employed the preformed Pd(II) catalyst $[Pd_2Cl_2(PPh_3)_2]$ with the additive Bu_4NBr in the presence of the weak base, Li_2CO_3. Preliminary results confirmed that transmetalation of $Bu_3SnSiMe_3$ by the vinylpalladium triflate intermediate **I** gave the arylpalladium vinyl stannane **II**, seemingly, as a consequence of the 'softer' nature of the stannyl group in comparison to the silyl group and hence, the stronger attraction to the 'soft' divalent palladium complex. The terminal intramolecular Stille coupling with the arylbromide afforded the expected cyclised product **174** in an excellent yield of 70%, however, significant amounts of the reduced product **175** were recovered.

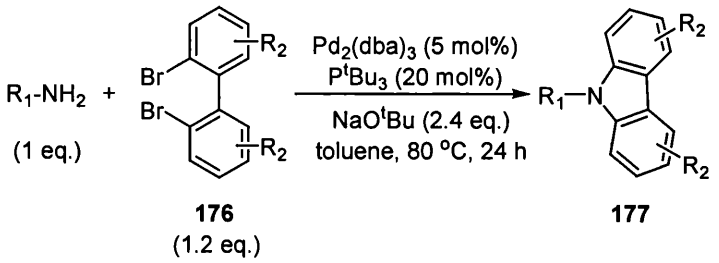


Scheme 4.3 Tandem transmetalation-intramolecular cyclisation

Upon exchange of $Bu_3SnSiMe_3$ for $Bu_3SnSnMe_3$, 8% of the reduced product and a non-reproducible yield of 64% of the cyclised product were achieved. This coupling sequence demonstrates the chemoselectivity of palladium catalysis as a result of the increased reactivity of the palladium towards oxidative addition to the vinyl triflate in comparison to the aryl bromide.

Tandem *C-N* bond formations

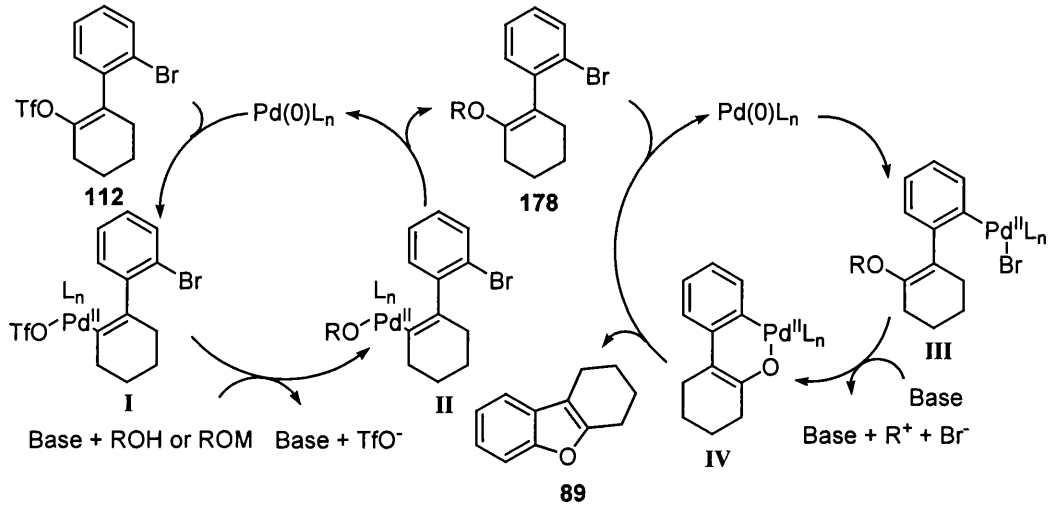
In 2003, Nozaki presented a new strategy towards the formation of carbazoles **177** *via* a palladium catalysed tandem *N*-arylation of substituted 2,2'-dihalobiphenyls **176** (**Scheme 4.4**). In this strategy the nitrogen atom in the carbazole comes from a primary amine, differing from other protocols that construct the carbazole ring from *o*-aminobiphenyl compounds. Based on the recent studies on the catalytic *N*-arylation of amines with organic halides, the catalyst generated from $Pd_2(dba)_3$ and P^tBu_3 successfully catalysed the cross-coupling of a primary amine and an aryl halide with subsequent cross-coupling of the resulting secondary amine with a second proximal aryl halide to form the carbazole ring. Electron-rich, electron-poor and electron-neutral functional groups were tolerated on both aromatic rings. The application of nickel or copper catalysts proved ineffective. This approach is complementary to the report from Willis and Brace that employs a mixed aryl bromide/vinyl triflate substrate to carry out the double *C-N* bond formation of primary amines.[1]



R_1= C_6H_5, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, *n*-C_8H_{17}
R_2= H, 5,5'-$(OMe)_2$, 4,4',5,5'-Me_4, 4,4',5,5'-$(MeO)_4$, 4,4'-$(CF_3)_2$, 4,4'-$(MeO)_2$

Scheme 4.4 Palladium-catalysed double *N*-arylation

Although there are no examples of tandem *C-O* bond formations, significant advances have been made towards the development and understanding of palladium-catalysed *C-O* bond formations and we hoped to adopt this methodology to realise a double *C-O* bond formation. **Scheme 4.5** depicts the anticipated catalytic cycle for our proposed palladium-catalysed tandem *C-O* bond formation. Initial oxidative addition of a palladium(0) species across the more labile vinyl triflate bond would give an intermediate organopalladium(II) complex **I**. Intermolecular nucleophilic addition of an oxygen surrogate **II** and subsequent reductive elimination would provide the masked enolate intermediate **178**. A second oxidative addition of the same palladium catalyst to the arylbromide bond would give the organopalladium(II) intermediate **III** with the timely deprotection of the *C-OR* group exposing a second nucleophilic alkoxide anion which can undergo an intramolecular nucleophilic substitution **IV**, followed by reductive elimination to give the benzofuran **89**.

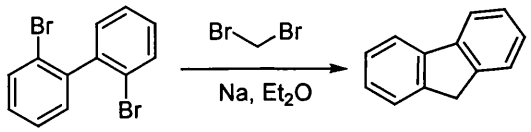


Scheme 4.5 Proposed catalytic cycle for tandem palladium-catalysed *C-O* bond formation

The search began for a suitable oxygen surrogate that could be effectively cross-coupled employing palladium catalysis and could be mildly cleaved *in-situ* exploiting conditions that are also compatible with the catalyst.

4.2 Surrogate Chemistry

The use of surrogate chemistry has been known for many years, with the discovery and application of novel reagents for the introduction of a single carbon fragment or a single heteroatom into a scaffold. One of the earliest examples was published in 1911 by Dobbie *et al.* describing the formation of fluorene **180** by a slow reaction of sodium with a mixture of 2,2'-dibromodiphenyl **179** and methylene dibromide in diethyl ether (**Scheme 4.6**).[6] In this case the methylene bromide acts as a carbon surrogate to form the methylene bridge between the two adjacent arylbromide groups.



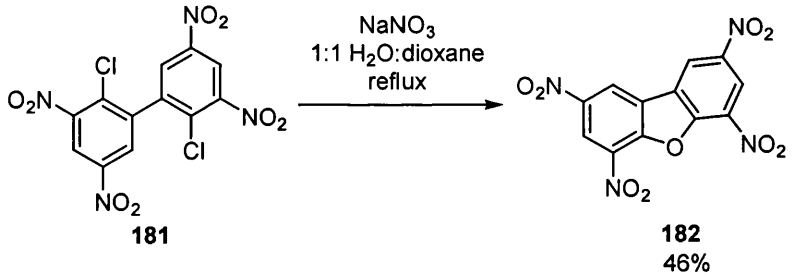
179 **180** 100%

Scheme 4.6 Methylene bromide as a carbon surrogate

There are many examples involving both carbon or nitrogen surrogate chemistry, however, the remainder of this chapter will focus on oxygen surrogate chemistry.

Oxygen surrogates

In 1943, Case and Shrock Jr. reported the formation of the unexpected cyclic biaryl ether **182**. This was prepared by the nitration of the dichlorobiphenyl derivative **181** using sodium nitrite in aqueous dioxane at elevated temperatures (**Scheme 4.7**). Mechanistically, water acts as an oxygen donor in a S_NAr type substitution reaction with subsequent cyclisation. In 1983, Maxer *et al.* described the synthesis of a similar tetrachloro-substituted dibenzofuran by pyrolysis of polychlorinated biphenyl congeners in 5 seconds at 550-600 °C in a sealed borosilicate ampule.[7] In this instance, oxygen itself acts as the oxygen donor with evolution of chlorine, hydrogen or HCl gas allowing the 38 positional isomers to be synthesised.

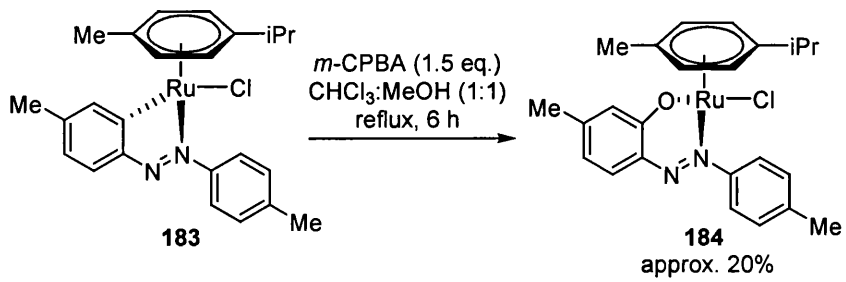


Scheme 4.7 Cyclisation of 2,2'-dichloro-3,3',5,5'-tetranitrobiphenyl **181**

Peroxides are also a valuable source of oxygen, being employed for epoxidations of alkenes and α,β-unsaturated ketones as well as oxidations of amines to oximes or insertion of oxygen into *C-H* bonds to form alcohols for example: hydrogen peroxide, *tert*-butyl hydroperoxide (TBHP),[8] trifluoroperoxyacetic acid[9] and *meta*-chloroperbenzoic acid (*m*-CPBA) are often the reagents of choice. Dimethyldioxirane has also been successfully developed as a reagent for the insertion of oxygen into unactivated *C-H* bonds of alkanes.[10] The following examples demonstrate the use of modified oxygenation reagents, exploiting peroxide chemistry for the insertion of oxygen into *C-X* and *C-M* bonds.

Gordon and Espenson described just one application of methyltrioxorhenium as an effective catalyst for oxidation reactions that exploit hydrogen peroxide.[11] They employed the catalyst for the oxidation of organosilanes to the corresponding silanols, avoiding the use of acid or base that would easily dimerise them. A subsequent communication by Chang *et al.* described an alternative transition-metal catalysed strategy for the mild oxidation of silanes using the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ under an aerobic or oxygen atmosphere, this time exploiting water as an oxygen source to give the desired silanols in excellent conversions in only 10 minutes.[12]

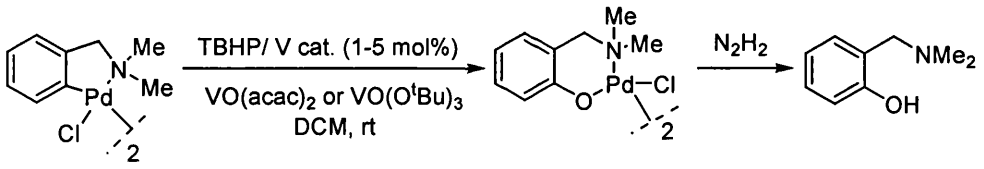
Regiospecific insertion of oxygen into a ruthenium-carbon bond is relatively rare. One example reported by Chakravarty *et al.* described oxygen insertion into an *Ar-Ru* bond to convert an azophenyl ligand **183** into an azophenol ligand **184** utilising *m*-CPBA as the oxygen source (**Scheme 4.8**).[13]



Scheme 4.8 *m*-CPBA oxidation of an *Ar-Ru* bond

Previous reports from Bandyopadhyay *et al.* described the *o*-hydroxylation of azobenzene derivatives based on a reaction sequence of cyclopalladation and subsequent oxygen insertion into the *Pd-C* bond with *m*-CPBA.[14-17] They later describe the use of iodosylbenzene[18] as an effective oxygen donor to carry out the analogous reaction (*cf.* **Scheme 4.8**).[19]

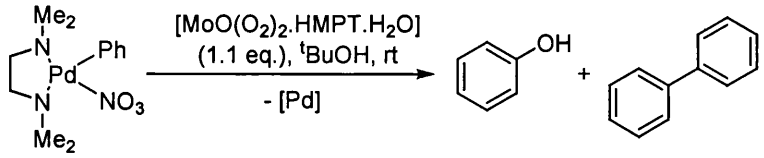
The group of van Koten outlined methodology towards the oxygenation of organopalladium complexes by inorganic and organic peroxides, highlighting the oxygen insertion into the palladium-carbon bond employing a vanadium peroxide catalyst[20] (**Scheme 4.9**), or stoichiometric quantities of a molybdenum peroxide (**Scheme 4.10**).[21] **Scheme 4.9** depicts the oxygenation of a cyclopalladated *N,N*-dimethylbenzylamine complex **185**, applying a catalyst generated from TBHP and either $VO(acac)_2$ or $VO(O^tBu)_3$ to give the *ortho*-substituted phenol **186** upon reductive work-up with hydrazine. TBHP alone showed sluggish reactivity. They observed an increase in the rate of oxygenation with an increase in nucleophilicity of the metal centre indicating that, in this system, the catalyst was a source of electrophilic oxygen. They therefore proposed that the active catalyst was very likely to be the vanadium(V) *tert*-butyl peroxo species, $VO(O_2{}^tBu)(O^tBu)_2$, reacting *via* a Pd(IV) oxo species (*cf.* Sharpless epoxidation).[22]



Scheme 4.9 Vanadium peroxide catalysed oxygenation of an organopalladium species

Alkoxides can effectively transform alkyl halides into the corresponding ethers *via* direct substitution and deprotection either simultaneously or in the latter stages of a synthesis, to expose a hydroxyl functional group. At the time of van Koten's research in 1993 there were deemed no satisfactory methods for the direct alkoxylation of *C-M* bonds. They discovered that activation of organopalladium complexes by the molybdenum peroxide $[MoO(O_2)_2.HMPT.H_2O]$ was sufficient for the direct coupling of alcohols to complexed carbocations (**Scheme 4.10**). They successfully coupled methanol, ethanol and benzyl alcohol to various palladated carbon atoms to give the

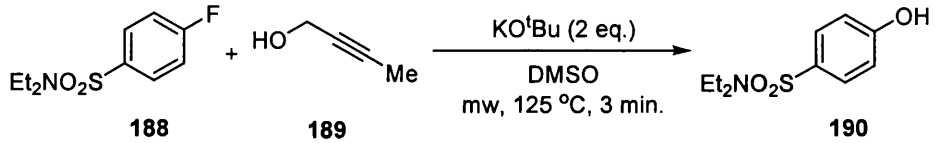
alkyl ethers in good yields. Direct hydroxylation was observed in the reaction of *tert*-butanol with the phenylpalladated complex **187**.



187 58% 25%

Scheme 4.10 Oxygenation of palladium complex carbocation by molybdenum peroxide

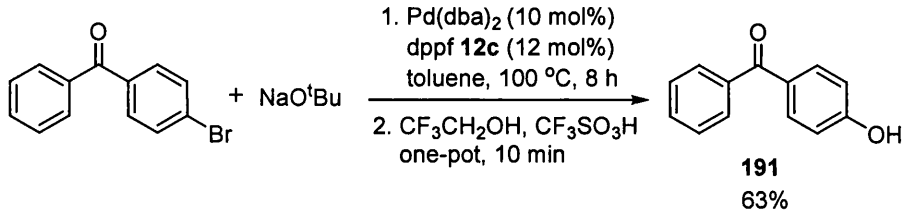
Methodology is well established for the conversion of aryl fluorides into the corresponding phenols.[23] The more common methods employ a two-step approach involving displacement of the fluoride anion by an alkoxide followed by cleavage of the resulting aryl alkyl ether to give the desired phenol.[24,25] A report by Levin and Du in 2002 disclosed a one-pot protocol for the synthesis of phenols **190** from aryl fluorides **188** *via* the S_NAr displacement of the fluoride anion by the propargylic alcohol, 2-butyn-1-ol **189** (**Scheme 4.11**).[26] Consecutive *in-situ* isomerisation to the allenyl ether and hydrolysis gave the phenol in good yield.



188 **189** (2 eq.) **190** 85%

Scheme 4.11 S_NAr displacement of arylfluorides by propargyl alcohols to give phenols

Several groups have described alternative palladium catalyst systems that promote the cross coupling of sodium *tert*-butoxide with aryl halides, the first example was reported in 1996 by the group of Hartwig (**Scheme 4.12**).[27] They observed the intermolecular formation of *tert*-butyl aryl ethers from electron deficient aryl bromides and NaO^tBu in the presence of a catalyst generated from $Pd(dba)_2$ and dppf **12c**. They successfully isolated the phenol adduct **191** in reasonable yield after treatment of the crude *tert*-butyl aryl ether with 2,2,2-trifluoroethanol and a catalytic amount of triflic acid, constituting a one-pot preparation of phenols from aryl bromides.



Scheme 4.12 Palladium-catalysed one-pot synthesis of phenols

Alternative systems were sought that could encompass a wider range of starting aryl halides, however preliminary studies showed that the ligands dppe, BINAP, dppp and dppbz were less effective than dppf **12c**. Shortly afterwards they demonstrated the application of this protocol to electron deficient aryl chlorides.[28] Buchwald reported the cross-coupling of primary and secondary alcohols, as well as NaO^{t}Bu, with electron-deficient and electron-poor aryl bromides, as well as electron deficient aryl chlorides, in the presence of a catalyst generated from $Pd_2(dba)_3$ and Tol-BINAP in toluene at elevated temperatures.[29] Much reduced catalyst loadings were applied [Pd:L 1.5:3.6 mol%]. Subsequent catalyst systems were discovered when new ligands were made available. Hartwig reported an improved reactivity employing d^{t}bpf **12b** as ligand,[30] and Buchwald reported several of the biphenylphoshino ligands (**3b**, **5b** and Dave-phos **4a**) to be effective.[31] More recently, Buchwald has discovered a milder catalyst generated from CuI and 1,10-phenanthroline to effectively cross-couple alcohols with aryl iodides in the presence of the mild base Cs_2CO_3, although elevated temperatures of 110 °C were still required.[32]

Recent reviews by Muzart give a comprehensive overview of palladium-catalysed cross-coupling reactions of alcohols.[33]

Silanoates as Oxygen donors

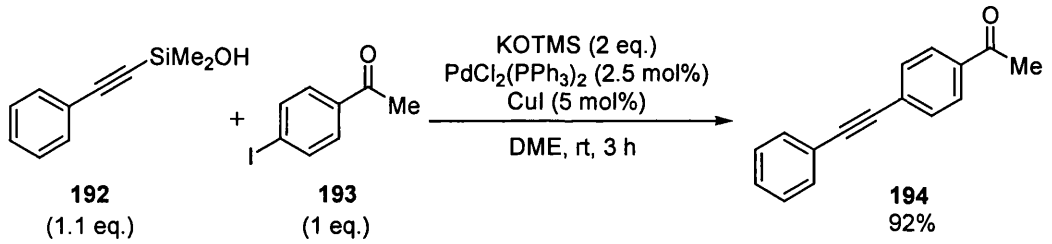
The silyl ether functional group has been well established for its use in the protection of hydroxyl groups, and as a consequence there is a vast quantity of literature surrounding the subject.[34,35] Only a relevant selection of methods for their formation and deprotection will be discussed.

Silyl ethers can be readily formed and cleaved under mild conditions,[36,37] and their stability finely tuned by varying the substituents on silicon.[38] In general, the relative stability towards acid-catalysed solvolysis is Me_3Si < Et_3Si < ^{t}BuMe$_2$Si < ^{i}Pr$_3$Si < ^{t}BuPh$_2$Si, and towards base-catalysed solvolysis is Me_3Si < Et_3Si < ^{t}BuMeSi = ^{t}BuPh$_2$Si < ^{i}Pr$_3$Si.[39] Fluoride reagents (*eg.* TBAF, H_2SiF_6, CsF, HF/pyridine, KF/Al_2O_3[40]) are also

widely applied to the cleavage of silyl ethers as silicon has a high affinity for fluorine, and as a direct result of the strength of the Si-F bond (810 $kJmol^{-1}$ Si-F *cf.* 530 $kJmol^{-1}$ Si-O) the silyl groups can be selectively removed. Consequently, a series of commercially available trimethylsilanoate-based reagents that are stable solids have been recognised as hydroxide anion equivalents soluble in organic solvents.

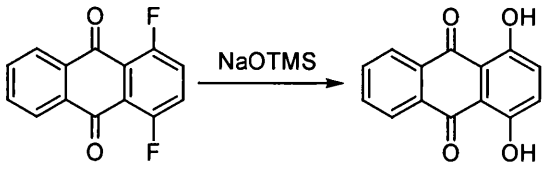
Potassium trimethylsilanoate has been frequently used in the preparation of anhydrous carboxylate salts from esters and acid chlorides-a reaction which was introduced by Laganis and Chenard in 1984.[41] Since then, several applications of trimethylsilanoates have been developed *eg.* racemisation-free hydrolysis of base sensitive α-hydroxy amino acids[42] and dienoate esters,[43] cleavage of 1,3-oxazolidin-2- or 5-ones and benzyloxycarbonyl groups,[44] or as nucleophiles in a nucleophilic Michael-type addition to 1-(phenylthio)-1-nitroalkenes.[45]

Denmark and Tymonko described the potassium trimethylsilanoate promoted cross-coupling of alkynylsilanols with aryl halides catalysed by both $PdCl_2(PPh_3)_2$ and CuI (**Scheme 4.13**).[46] A range of electron-rich, electron-neutral and electron-poor aryl iodides **193** were successfully coupled with dimethyl(1-heptynyl)silanol **192** at room temperature within 3 hours to give the corresponding aryl alkynes **194** in excellent yields. They found that KOTMS promotion was superior than TBAF promoted cross coupling especially in the presence of other silyl protecting groups. The exact mechanism remains elusive although the presence of silanol and copper iodide were crucial to the success of the reaction, thus providing a viable alternative to the traditional Sonogashira reaction.



Scheme 4.13 Cross coupling of alkynylsilanols with aryl halides promoted by KOTMS

Krapcho and Waterhouse described an effective use of NaOTMS in the preparation of phenols from aryl fluorides (**Scheme 4.14**).[47] S_NAr displacement of the fluoride anion by the silanoate gave the intermediate aryl silyl ether, and the resulting *in-situ* deprotection by the newly generated fluoride anion gave the free phenol.



78%

Scheme 4.14 Synthesis of phenols from aryl fluoride and sodium trimethylsilanoate

Hartwig and Mann described the palladium and nickel catalysed coupling of electron-deficient aryl bromides with NaOTBDMS at elevated temperatures (**Scheme 4.15**).[28] Reactions of an aryl bromide and NaOTMS, NaOTES or NaOTPS, catalysed by the superior nickel catalyst generated from $Ni(COD)_2$ and dppf, did not result in the formation of silyl aryl ether. They stress the instability of the resulting *tert*-butyldimethylsilyl aryl ethers to hydrolysis upon column chromatography, resulting in recovery of the corresponding phenols.

$Pd(dba)_2$ (10 mol%), dppf **12c**, toluene, 120 °C, 2 h 76%
$Ni(COD)_2$ (10 mol%), dppf **12c**, toluene, 95 °C, 2 h 95%

Scheme 4.15 Palladium-catalysed coupling of metal silanoates with aryl halides

Fluoride deprotection of silyl enol ethers is compatible with palladium catalysis as *in-situ* cleavage of a TBDMS silyl enol ether with subsequent palladium-catalysed Stille cross-coupling in the presence of Bu_3SnF has been reported,[48] although milder conditions for selective cleavage of aryl silyl ethers are continually sought. One investigation by Wang has lead to the development of mild conditions for the cleavage of aryl TBS ethers in the presence of Cs_2CO_3 in DMF-H_2O at room temperature to give the corresponding phenols in high yields.[49] The conditions were selective for aryl TBS ethers and did not cleave alkyl TBS, phenyloxycarbonyl or tetrahydropyranyl protected alcohols. Another by Kondo *et al.* describes the catalytic activation of silylated nucleophiles employing $^tBuP_4$ as a base.[50] The conditions are mild although not selective, as both TMS and TBDMS silyl aryl ethers were cleanly cleaved in the presence of only 10 mol% of the base in either DMF or DMSO at room temperature. Protection and deprotection of alcohols by triethylsilane can be effected in the presence of a $PdCl_2$ catalyst at room temperature or at elevated temperatures in ethanol.[51]

Deprotection of the silyl ether relies upon the *in-situ* production of molecular hydrogen by the spontaneous reaction of ethanol and triethylsilane catalysed by $PdCl_2$.

4.3 Discovery of an oxygen surrogate compatible with palladium catalysis

We selected the coupling of **112** as our test substrate (*cf. C-N* bond formation)[1] and focussed on metal alkoxide and metal silanoate reagents as the initial oxygen surrogates. **Table 4.1** charts the most promising preliminary results obtained.

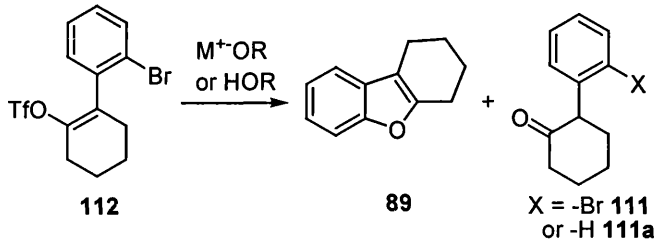


Table 4.1 Investigation of oxygen surrogate[a]

Entry	Ligand	Oxygen donor (base)	Eq.	Additive	Eq.	Conv. (%)
1	Xantphos	NaO^{t}Bu	1.75	-	-	**111a**
2	**12c**	NaO^{t}Bu	3		-	27
3	HP^{t}Bu$_3$BF$_4$	H_2O_2	1.5 or 3	-	-	starting materials
4	HP^{t}Bu$_3$BF$_4$	H_2O	3	KOH	3	starting materials + trace **111**
5	Xantphos	NaOTMS	1.5	-	-	trace **89**
6	Xantphos	NaOTMS	3	-	-	20% **89**
7	DPEphos	NaOTMS	3	-	-	**111**
8	**3b**	NaOTMS	3	-	-	30% **89**
9[b]	Xantphos	KOTMS	3	-	-	**111**
9	**3b**	LiOTMS	3	-	-	starting material
11	**3b**	NaOTMS	3	15-crown-5	0.2	unknown mixture
12	**3b**	KOTMS	3	18-crown-6	0.2	**111** + **111a** + < 5% **89**
13[c]	**3b**	TMSOH[52]/ Cs_2CO_3	3	-	-	**111** + **112**
14	**3b**	NaOTMS	3	$ZnEt_2$	1	**111** + **112**
15[d,e]	HP^{t}Bu$_3$BF$_4$	TMSOH[52]	3	$ZnCl_2$	1.5	unknown mixture

Conditions: **a**: arylated ketone (1 eq.), $Pd_2(dba)_3$ (5 mol%), ligand (12 mol%), toluene or dioxane, 100 °C, 24 h; **b**: ligand **3b** gave ketone product; **c**: TESOH and TBDMSOH gave starting materials only; **d**: DMF as solvent; **e**: ligand **3b** gave a mixture of products.

Employment of NaO^{t}Bu as the nucleophilic oxygen source and base in the presence of a catalyst generated from $Pd_2(dba)_3$ and Xantphos gave undesired debromination of the starting triflate (entry 1, **Table 4.1**). Pleasingly, exchange of Xantphos for **12c** gave the expected benzofuran, albeit in a low yield of 27% (entry 2). Buchwald attributed the low yields obtained for the palladium-catalysed cross coupling between amines and electron-poor aryl triflates to an increased ease of attack of the sodium *tert*-butoxide base, on the sulfur of the triflate, in the activated system. This resulted in cleavage of the triflate and formation of sodium phenoxide.[53] A control reaction was carried out without any catalyst to verify that the alkoxide base was not hydrolysing the triflate back to the ketone and, as a consequence, not reacting under catalysis. A mixture of degradation products was observed as well as trace amounts of the ketone product confirming that NaO^{t}Bu is incompatible with vinyl triflates.

Several unrefined attempts to couple hydrogen peroxide and H_2O as oxygen donors were abandoned as the majority of the starting material was recovered (entries 3 and 4). Our attention turned to the application of metal silanoates as they have been shown to be compatible with similar phosphine based palladium catalyst systems.[28] Employment of sodium silanoate (1.75 eq.) in the presence of the catalyst [$Pd_2(dba)_3$, Xantphos] gave trace amounts of the desired benzofuran (entry 5). Increasing the amount of silanoate used to 3 eq., to allow the silanoate to act as both oxygen donor and base more efficiently, gave the benzofuran in 20% yield (entry 6). Previous studies found that use of the ligand DPEphos gave a more effective catalyst system for the cyclisation of *O*-enolates onto aryl bromides (**Chapter 3**). Surprisingly, substituting Xantphos for DPEphos only led to recovery of the ketone analogue suggesting cross-coupling of the silanoate with the vinyl triflate was sluggish and catalyst activity and longevity was questionable (entry 7).

Previously within the Willis laboratory, it has been shown that a catalyst generated from $Pd(OAc)_2$ (5 mol%) and di-*tert*-butylphosphinobiphenyl ligand **3b** (7.5 mol%) effectively cross-coupled sodium trialkylsilanoates with substituted arylbromides (in toluene at 60 °C over 16 hours) yielding the corresponding mixed arylalkylsilyl ethers in moderate conversions. We had also observed that a catalyst generated from $Pd_2(dba)_3$ and ligand **3b** with Cs_2CO_3 as base (at 100 °C overnight) executed the *O*-enolate cyclisation of the intermediate α-arylated ketone **111** to the benzofuran **89** in 100% conversion. Encouragingly, a positive result was obtained employing this catalyst system [$Pd_2(dba)_3$, **3b**] for the double insertion reaction, producing the cyclised

benzofuran in a respectable yield of 30%, although the remaining reaction mixture was solely degradation products (entry 8).

Counter-ion effects

Counter-ions can change the rate of attack of a nucleophile by altering its immediate environment. The greater the Lewis acid character of the cation the tighter the ion pair and in general, the Lewis acid character of the cation decreases as you descend a group in the periodic table eg. Li > Na > K > Cs. The more exposed the nucleophile, the easier it can attack an electrophilic centre, so in theory LiOTMS should be less reactive than KOTMS. Hartwig and Mann noted a distinct effect of the counter-ion in the reaction between aryl halides and *tert*-butoxide showing that the sodium counter-ion proved critical in the presence of a palladium or nickel based catalyst, with dppf **12c** as the ligand.[28] Neither lithium and potassium *tert*-butoxide afforded any significant amount of the desired ether.

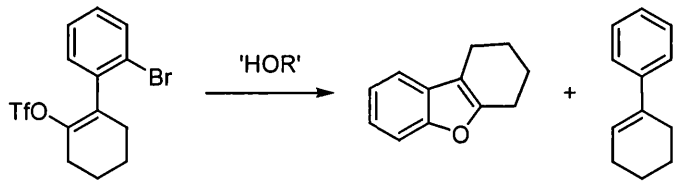
Unfortunately, employing potassium trimethylsilanoate in combination with a catalyst generated from $Pd_2(dba)_3$ and Xantphos gave only the ketone intermediate. Sodium trimethylsilanoate, in comparison, produced the benzofuran product in 20% yield; again no starting material was recovered (entries 9 and 6 respectively, **Table 4.1**). As expected employment of lithium trimethylsilanoate gave unreacted starting material only, indicating that the nucleophilicity of the silanoate plays a key role in the cross-coupling strategy (entry 10). Employment of crown ethers to sequester the counter ions should give more nucleophilic silanoate ions and make the generated bromide anions uncoordinated, promoting desilylation of the intermediate vinyl or aryl silyl ether. Unfortunately, employment of 15-crown-5 in combination with sodium trimethylsilanoate gave an unknown mixture of products (entry 11), and employment of 18-crown-6 in combination with potassium trimethylsilanoate gave a mixture of the ketone and debrominated products, with trace amounts of the benzofuran (entry 12). We therefore reasoned that substituting the counter-ion for cesium or zinc could give intermediate behaviour and less degradation products.

Hartwig described the use of zinc trimethylsilylamide as a mild ammonia equivalent and base for the palladium-catalysed amination of aryl halides and triflates, tolerating base sensitive functionality.[54,55] Acid hydrolysis of the silylamide gave the primary arylamines. *In-situ* formation of cesium trimethylsilanoate from trimethylsilanol and Cs_2CO_3 gave ketone and starting material only (entry 13). It may be possible that

formation of hexamethyldisiloxane *in-situ* under the basic conditions could slow the rate of reaction. Therefore, we employed two methods for the *in-situ* formation of the zinc derivative, neither involving base. The combination of NaOTMS/$ZnEt_2$ gave an inefficient reaction (entry 14) and, unfortunately, the combination of trimethylsilanol and zinc dichloride in the presence of catalysts generated from both $HP^tBu_3BF_4$ and **3b** with $Pd_2(dba)_3$ gave unknown mixtures of products (entry 15).

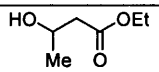
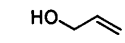
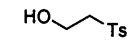
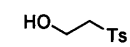
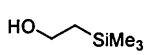
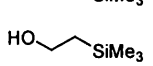
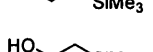
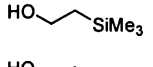
4.3.1 Alcohols as oxygen surrogates

We chose to investigate alternative oxygen sources, exploiting alcohol substrates that can be cleaved upon formation of the corresponding aryl vinyl ether.



112 **89** **195**

Table 4.2 Scope of alcohol oxygen surrogate[a]

Entry	Oxygen surrogate	Ligand	Base	Eq.	Additive	Eq.	Conv. (%)
1		**12c**	Cs_2CO_3	3	-	-	9 **89**
2[b]		**3b**	Cs_2CO_3	3	-	-	25 **195**
3[c]		DPEphos	Cs_2CO_3	3	-	-	unknown mixture + **195**
4[d]		$HP^tBu_3BF_4$	Cs_2CO_3	3	-	-	32 **89**
5[e,f]		$HP^tBu_3BF_4$	Et_3N	2	TBAF	1	unknown mixture
6[f]		$HP^tBu_3BF_4$	Cs_2CO_3	2	TBAF	1	41 **195**
7[f]		$HP^tBu_3BF_4$	CsF	1.5	CsF	1.5	unknown mixture
8		$HP^tBu_3BF_4$	NaO^tBu	3	-	-	77 **195**

Conditions: **a**: oxygen surrogate (2 eq.), $Pd_2(dba)_3$ (5 mol%), ligand (12 mol%), dioxane or toluene, 100 °C, 20-24 h; **b**: alcohol (1.2 eq.); ligands DPEphos and **3b** gave none of the desired product; **c**: ligand **12c** gave an unknown mixture; **d**: application to tosyl alcohol equivalent gave no positive results; **e**: Et_3N (3 eq.) without TBAF gave starting materials only; **f**: alternative bases: DBN (3 eq.), Et_3N (3 eq.) gave unknown mixtures.

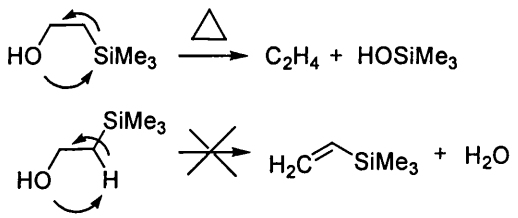
Pleasingly, our first attempt employing an ester tethered primary alcohol and catalyst generated from $Pd_2(dba)_3$ and ferrocene based ligand **12c** gave the desired benzofuran, albeit in 9% yield (entry 1, **Table 4.2**). Thus far, a clean reaction devoid of degradation had not been achieved using the ferrocene-based ligand. However, in this case, exchange of the ligand for DPEphos or **3b** gave none of the desired products.

Surprisingly, employment of allyl alcohol gave none of the desired product although 25% of a reduced product **195** was recovered (entry 2).

Presumably, the use of 2-tosylethanol[56] or trimethylsilylethanol[57,58] would avoid formation of η^3-allylpalladium intermediates.[59] Application of our original catalyst system [$Pd_2(dba)_3$, DPEphos] in combination with the weaker base Cs_2CO_3 to the cross-coupling of 2-tosylethanol gave an unknown mixture of products with evidence of the reduced product (entry 3).[60] Substitution of DPEphos by ferrocene **12c** gave a negative result. Pleasingly, employment of Fu's salt $HP^tBu_3BF_4$ gave the desired benzofuran in a moderate yield of 32% (entry 4). Nucleophilic bases have been successfully used to eliminate arenesulfinic acid from alkyl aryl sulfones,[61] however, the presence of a triflate subunit prohibits their involvement.

Therefore, initial reactions were undertaken employing trimethylsilylethanol and a catalyst generated from $Pd_2(dba)_3$ and $HP^tBu_3BF_4$ in combination with alternative base and fluoride sources for cleavage of the silyl group.[62] Use of triethylamine in combination with TBAF gave an unknown mixture of products, however, without TBAF only unreacted starting materials were recovered (entry 5). Substitution of triethylamine for the inorganic base Cs_2CO_3 gave the reduced product **195**, although in an improved yield of 41% (entry 6). An attempt to exploit CsF as both the base and fluoride source gave an unknown mixture of products (entry 7),[63] as did alternative bases, DBN and triethylamine. Surprisingly, utilising NaO^tBu to perform basic cleavage of the silyl moiety gave the reduced product in an enhanced yield of 77% (entry 8).

We were unsure how this reduced product was being formed in such abundance. Taylor published a kinetic study for the elimination of 'free' trimethylsilanol,[64] showing that the rate of elimination is governed by the formation of the stronger *Si-O* bond. Even at elevated temperatures there was no evidence of vinyltrimethylsilane (**Scheme 4.16**), so it therefore seemed unlikely that this was the reaction pathway.

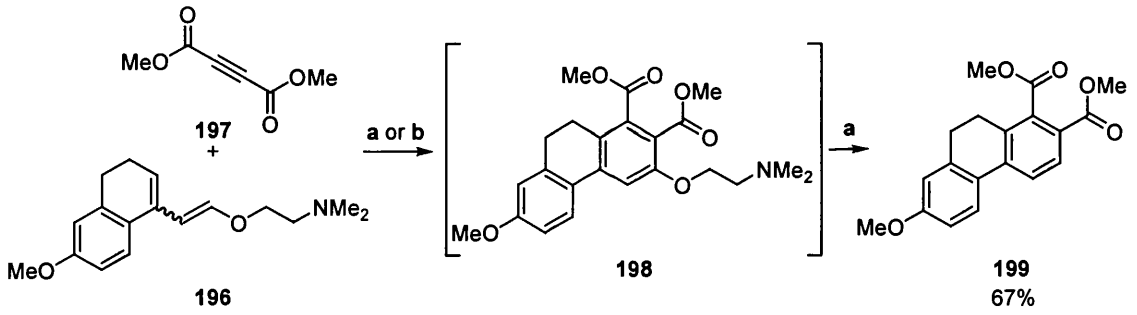


Scheme 4.16 Elimination sequence of trimethylsilylethanol

Hydroformylation of aryl and enol triflates by palladium catalysis[65] is well known employing organosilanes,[66,67] organostannanes[68,69] and formic acid[70,71] as the reductants.

Another effective deoxygenation process involves carrying out these palladium-catalysed reactions in CH_3OD or DCO_2D to incorporate deuterium labels.[72,73] It is plausible that the alcohol is the source of hydrogen. Again, it is possible that we recovered reduced product because the rate of reductive elimination to form *C-O* bonds was somewhat slower than *β*-hydride elimination. The involvement of a mono-phosphine ligand may allow formation of an unsaturated organopalladium intermediate and thus favour the *β*-hydride elimination pathway.

Stadler *et al.* reported the synthesis of linear 1,3-butadienes *via* a terminal chelation-controlled Heck vinylation involving cross-coupling of an amino-tethered vinyl ether and vinyl triflate substrate.[74] To demonstrate their utility, the 1,3-butadienes **196** were used in a microwave assisted Diels-Alder reaction with dimethyl acetylenecarboxylate (DMAD) **197** to give the corresponding aromatic compounds **199** (**Scheme 4.17**). Unfortunately, the elimination of the 2-dimethylaminoethanol portion was unavoidable and only under reductive conditions (addition of 3 eq. of hydroquinone) did they manage to isolate the expected aromatic compound **198**. No explanation as to why this happened was offered.



Conditions: **a**: CH_3CN, MW, 120 °C, 60 min.; **b**: **a** + hydroquinone (3 eq.)

Scheme 4.17 Accidental removal of dimethylaminoethanol

Additional experimental evidence is required to determine why this is apparently the favoured reaction pathway and to tune the catalyst conditions to avoid this undesirable reactivity.

4.4 Concluding Comments

We have shown that it is possible to execute a tandem palladium-catalysed *C-O* bond forming reaction exploiting oxygen surrogate chemistry. Mild reaction conditions that effect the selective reduction of both a vinyl triflate and an aryl halide moiety were established, although only moderate yields of product were obtained. This strategy is

very much in its infancy and will be explored further to develop and understand more fully the preliminary results.

4.5 References

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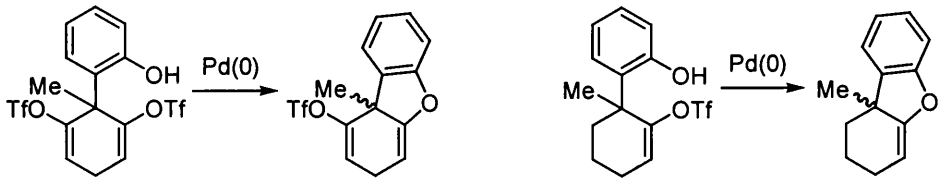
Chapter 5 Palladium Catalysed Intramolecular Aryl Enol Ether Synthesis from Vinyl Triflates

A system for the intramolecular preparation of aryl enol ethers by palladium-catalysed cyclisation of phenols and vinyl triflates was sought for three reasons 1) to explore the intramolecular variation of the intermolecular system previously established 2) to expand the scope of the ketone α-arylation chemistry to include more readily available *o*-halophenol derivatives and 3) to gain access to alternative substrates for palladium-catalysed desymmetrisations.

5.1 Intramolecular palladium-catalysed cross-coupling of phenols and vinyl triflates

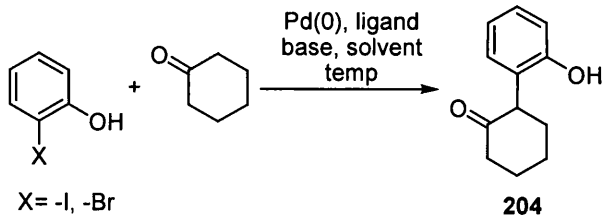
Scheme 5.1 depicts the proposed intramolecular desymmetrisation of an analogous α-phenol *bis*-vinyl triflate **200** to give the aryl enol ether **201** (*cf.* **Chapter 2**). First we wanted to prepare the simplified α-phenol mono-vinyl triflate **202** and investigate whether or not the key *C-O* bond construction to give aryl enol ether **203** was feasible.



200 **201** **202** **203**

Scheme 5.1 Proposed methodology for intramolecular palladium-catalysed *C-O* bond formation

Unfortunately, no preparative methods for the α-arylation of ketones with *o*-halophenols had been established. Previous reports by Buchwald demonstrated the success of palladium catalyst systems for the α-arylation of ketones with *m*- and *p*-bromophenols but without success for *o*-halophenols.[1] Thus far there have been only a few functional groups tolerated in the *o*-position of the aryl group including -F, -Me, -OMe and -CF_3.[2,3] Preliminary studies towards the α-arylation of cyclohexanone with *o*-iodo- or *o*-bromophenol employing catalysts generated from $Pd_2(dba)_3$ and ligands Xantphos, DPEphos or $HP^tBu_3BF_4$ with Cs_2CO_3, NaO^tBu or NaHMDS as base at 80-100 °C overnight resulted in the recovery of starting materials and aldol products only (**Scheme 5.2**).

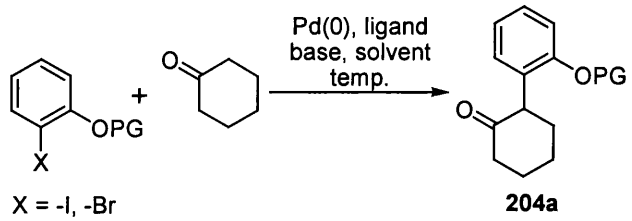


Scheme 5.2 Palladium-catalysed α-arylation of cyclohexanone by *o*-halophenol

The *o*-alkynylation of *o*-halophenols has also been developed over the last decade with both protected and unprotected phenols.[4] Flynn and Chaplin described the use of methylmagnesium chloride as a base for the deprotonation of *o*-iodophenol to give a masked magnesium phenolate, thus preventing the impromptu cyclisation of the *o*-alkynylphenols upon their formation by palladium catalysis.[5] We modified this approach by employing *tert*-butylmagnesium chloride, however, none of the desired α-arylated cyclohexanone or Grignard addition products formed, although starting *o*-iodophenol and aldol products were observed. Chen *et al.* discovered that the palladium-catalysed coupling between *o*-iodoaniline and cyclohexanone in the presence of $Pd(OAc)_2$ and an amine base, DABCO, in DMF at 105 °C gave the corresponding indole in one-step.[6] We did not observe any formation of the benzofuran product.

5.1.1 Phenol protection

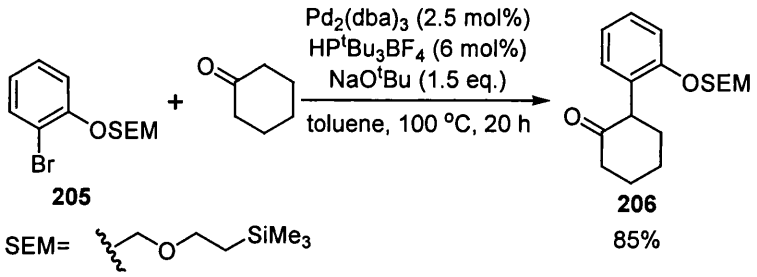
Intermolecular *ortho*-arylation of phenols is known employing rhodium[7] and palladium catalysis.[8,9] The *ortho*-arylation of salicylaldehydes *via* palladium catalysed cross-coupling of both arylstannanes[10] and boronic acids,[11] in Stille and Suzuki reactions respectively, have been reported. The inability to α-arylate ketones with *o*-halophenols may be due to possible interactions of the hydroxyl and carbonyl groups in the organopalladium complex, therefore use of a suitable hydroxyl-protecting group would disable this interaction and allow the reaction to proceed. We required a protecting group that would be suitably stable under our palladium catalytic conditions but could be readily removed at a later stage in the synthesis, potentially in the presence of a vinyl triflate (**Scheme 5.3**).[4,12]



Scheme 5.3 Proposed strategy for α-arylation of ketones with *o*-halophenols

We discovered that the α-arylation of cyclohexanone with *o*-bromoanisole (a methyl protected phenol) in the presence of a catalyst generated from $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)-2'-methyl-biphenyl **5a** with NaO^tBu as base gave the desired product in a yield of 54%. Employing Xantphos as the ligand in place of **5a** gave only trace amounts of the product. Irrespective of this result, we endeavoured to find a more effective protecting group, pursuing more easily removable groups. An acyl protecting group[13] gave none of the desired product despite activating the aromatic ring to oxidative addition of the palladium(0) catalyst; perhaps it rendered the aryl group too sterically hindered for the ketone reductive elimination to occur. A ketal protecting group would remove steric hindrance from the *ortho*-position, however, attempts to synthesise the diphenyl ketal with acetone[14] or dimethoxypropane[15,16] by treatment with PPTS[17] (pyridinium *para*-toluenesulfonate) or PTSA[18] (*para*-toluenesulfonic acid) gave a myriad of inseparable products.

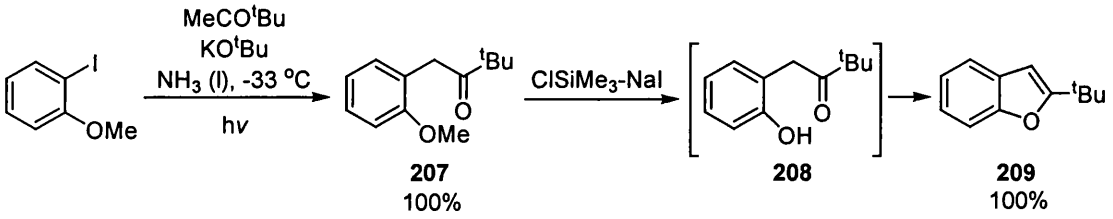
Several reports in the literature focus on the effectiveness of palladium catalysts for the cyclisation[19] and isomerisation/deprotection[20,21] of allyl protecting groups. Thayumanavan *et al.* reported very mild conditions for the deprotection of phenyl allyl ethers in the presence of $Pd(PPh_3)_4$, K_2CO_3 in MeOH at room temperature.[22] In the presence of our catalyst, α-arylation of 1-allyloxy-2-bromobenzene led to an undesirable mixture of isomers of both the starting aryl allyl ether and the α-arylated cyclohexanone, with no unprotected phenol observed. Therefore, we prepared a range of silyl protected *o*-iodophenol substrates[23] including TMS,[24] TES and TBDMS.[25,26] When they were subjected to our original α-arylation catalyst system [$Pd_2(dba)_3$, Xantphos, Cs_2CO_3, toluene, 100 °C] they gave none of the desired α-arylated cyclohexanone **204a**. There was also apparent cleavage of the protecting group. Substituting $HP^tBu_3BF_4$ for Xantphos also gave negative results. Alternative, more robust silyl protecting groups TMSE (2-(trimethylsilyl)ethyl), DMPSE (2-(dimethylphenylsilyl)ethyl) or the more recently reported TBDPSE (*tert*-butyldiphenylsilylethyl) group[27] have shown to be effective as phenol protecting groups, although they require strong acid or fluoride source for deprotection. We opted for the longer chain silyl SEM protecting group[28] (**205**) as it would minimise steric bulk around the *ortho*-position and it can be readily cleaved with aqueous acid,[29] iodine in methanol[30] or a fluoride source. Pleasingly, the desired α-arylated product **206** was synthesised in a reproducible yield of 85%, employing a catalyst generated from $Pd_2(dba)_3$ and $HP^tBu_3BF_4$ with NaO^tBu as base (**Scheme 5.4**).



Scheme 5.4 α-Arylation of cyclohexanone with SEM protected *o*-bromophenol

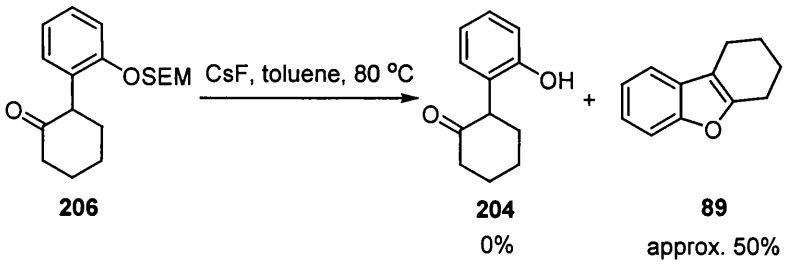
5.1.2 Phenol deprotection

In 1980, Beugelmans and Ginsburg described the synthesis of 2-substituted benzo[*β*]furans *via* a regiospecific radical $S_{RN}Ar$ reaction of *o*-iodoanisole and a ketone enolate (**Scheme 5.5**).[31] The intermediate α-arylated ketone **207** was isolated and treated with $ClSiMe_3$-INa in order to cleave the methoxy phenolic protecting group.[32] The hydroxyphenyl ketone **208** underwent spontaneous cyclodehydration to give the corresponding benzofuran **209** in quantitative yield. The equivalent reaction can also be achieved employing 48% HBr-AcOH but in lower yields as the final product polymerises under the strongly acidic conditions.[33] Alternatively, phenyl methyl ethers may be treated with a Lewis acid to remove the methyl protecting group, although fewer functional groups are tolerated.[34]



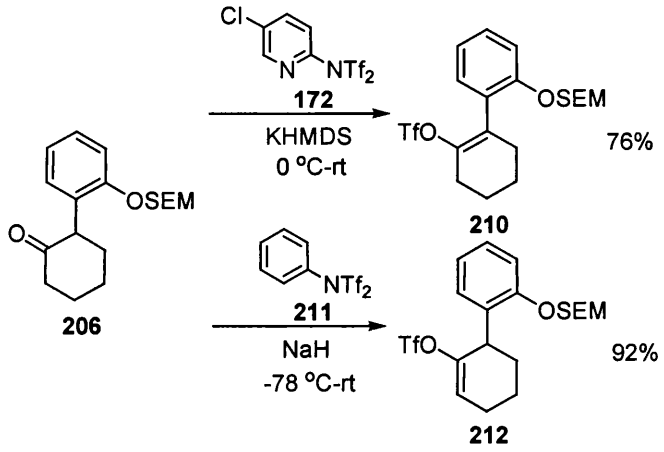
Scheme 5.5 Synthesis of benzofurans by a radical $S_{RN}Ar$ reaction of *o*-iodoanisole[31]

Preliminary attempts to deprotect the SEM group with cesium fluoride required elevated temperatures of 80 °C and, unsurprisingly, at these temperatures none of the desired phenol **204** was observed but complete conversion to the cyclised product **89**. This presumably occurred *via* a cyclodehydration pathway as previously observed by Beugelmans and Ginsburg[31] (**Scheme 5.6**).



Scheme 5.6 Fluoride deprotection of SEM

To avoid this cyclodehydration pathway we chose to transform the ketone **206** to the triflate **210** prior to the deprotection (**Scheme 5.7**). We successfully synthesised the more highly substituted triflate **210** in 76% yield following the established procedure for the triflation of the analogous bromo substrate **111** [pyridyl triflimide **172**,[35] KHMDS at 0 °C]. Slow addition of base (KHMDS) to a solution of the ketone **206** in THF at 0 °C allowed for the equilibration of the resulting enolate to the desired thermodynamic regioisomer which was then successfully trapped by the triflating agent **172** at 0 °C to room temperature over 18 hours.



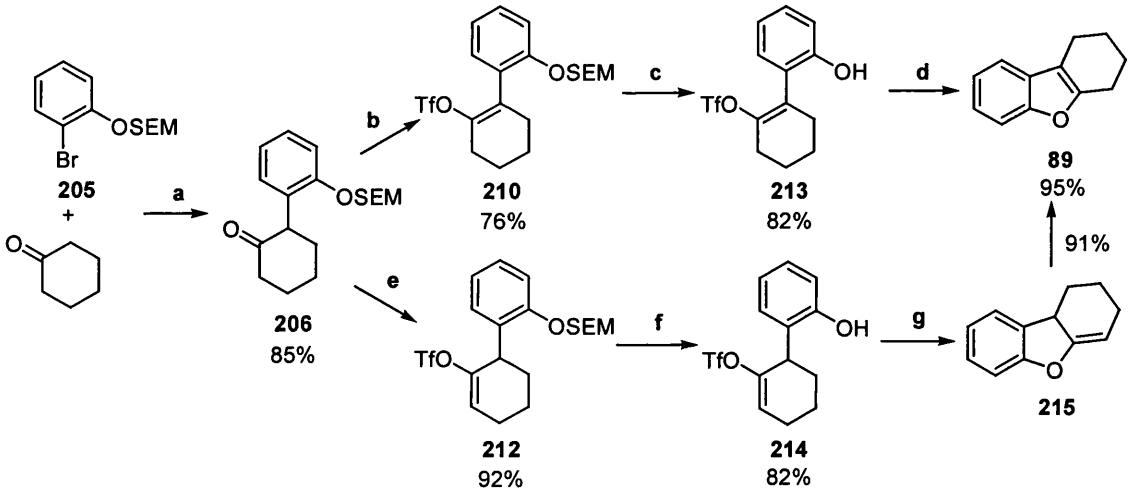
Scheme 5.7 Regioselective synthesis of kinetic and thermodynamic triflation products

Upon lowering the temperature of the reaction to -78 °C, we were able to isolate the less highly substituted kinetic regioisomer **212** in a more moderate yield of 67%. The speed of addition of base was not deemed important in this case, or the equivalents of base used, as the dominant enolate formed with strong base at lower temperatures is the desired kinetic regioisomer. Addition of the triflating agent at -78 °C effectively trapped the kinetic enolate without allowing for equilibration to the thermo-regioisomer. Surprisingly, exchange of the pyridyl triflimide **172** for the phenyl triflimide **211** and KHMDS for NaH as base gave the kinetic isomer in an improved yield of 92%. It was

very difficult to isolate the triflate product from the triflating agent as they tended to co-elute. Flash column chromatography and several recrystallisations were thus required to remove the triflimide. New techniques and reagents to overcome this issue are being explored within our laboratory *eg.* polymer-supported triflating reagents.[36]

At this stage we envisaged a one-pot deprotection and cyclisation employing cesium fluoride as both the fluoride source for deprotection of the SEM and base to drive the catalytic cycle. Unfortunately, the reaction did not give the desired benzofuran product with our original *O*-enolate cyclisation catalyst [$Pd_2(dba)_3$, DPEphos] but instead gave a mixture of starting material and unknown products. We needed to isolate the deprotected phenol intermediates in order to determine if this catalyst system was effective for the intramolecular cross-coupling reaction between phenol and vinyl triflate.

Scheme 5.8 depicts the successful reaction pathways for the synthesis of aryl enol ether **215** and benzofuran **89**. Both unprotected phenol regioisomers were isolated in an 82% yield when exposed to aqueous hydrochloric acid (1M or 2M) at an elevated temperature of 80 °C in 4-6 hours. Cesium fluoride is also effective giving comparable yields. Both regioisomers gave the respective cyclised products in excellent yields (>90%) when exposed to our original catalyst system [$Pd_2(dba)_3$, DPEphos, Cs_2CO_3].



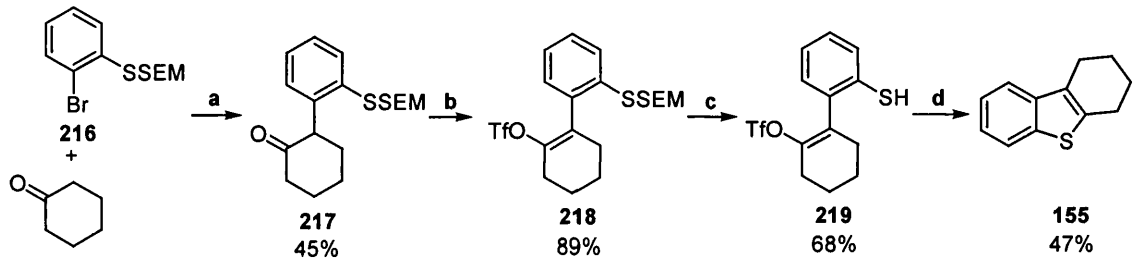
Conditions: **a**: ketone (1 eq.), halide **205** (1.2 eq.), $Pd_2(dba)_3$ (2.5 mol%), $HP^tBu_3BF_4$ (6 mol%), NaO^tBu (1.5 eq.), toluene, 100 °C, 20 h, 85%; **b**: ketone **206** (1 eq.), KHMDS (1.1 eq.), THF, 2-[*N,N-bis*(trifluoromethanesulfonyl)amino]-5-chloropyridine **172** (1.1 eq.), 0 °C to rt, O/N, 76%; **c**: vinyl triflate **210** (1 eq.), HCl (1M, 1.5 eq.), THF, 80 °C, 4 h, 82%; **d**: phenol **213** (1 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6 mol%), Cs_2CO_3 (1.5 eq.), dioxane, 100 °C, 20 h, 95%; **e**: ketone **206** (1 eq.), KHMDS (1.1 eq.), THF, 2-[*N,N-bis*(trifluoromethanesulfonyl)amino]-5-chloropyridine **172** (1.1 eq.), -78 °C-rt, O/N, 67%; or ketone **206** (1 eq.), NaH (1.1 eq.), THF, *N*-phenyl-*bis*(trifluoromethanesulfonimide) **211** (1.1 eq.), -78 °C to rt, O/N, 92%; **f**: vinyl triflate **212** (1 eq.), HCl (2M, 1.5 eq.), THF, 80 °C, 6 h, 82%; **g**: phenol **214** (1 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6 mol%), Cs_2CO_3 (1.5 eq.), dioxane, 100 °C, 20 h, 91% (yield based on isolated benzofuran **89**).

Scheme 5.8 Intramolecular palladium-catalysed enol ether synthesis

Although the non-conjugated aryl enol ether **215** was observed by crude NMR it could not be isolated as it isomerised to the fully conjugated benzofuran **89** upon Celite or silica purification. This would not be an issue when an α-quaternary carbon centre instead of an α-tertiary carbon centre is present in the starting substrate. Aryl enol ether **215** and benzofuran **89** were synthesised in 4 steps in 58% and 50% overall yield respectively.

5.2 Intramolecular palladium-catalysed cross-coupling of thiols and vinyl triflates

Having established the reaction parameters for the intramolecular cross-coupling of phenols and vinyl triflates we wanted to determine whether or not the conditions were transferable to the analogous *C-S* bond formation between thiols and vinyl triflates (**Scheme 5.9**). To the best of our knowledge, this would be the first report of a palladium-catalysed cross-coupling reaction between a thiol and a vinyl triflate.



Conditions: **a**: ketone (1 eq.), halide **216** (1.2 eq.), $Pd_2(dba)_3$ (2.5 mol%), $HP^tBu_3BF_4$ (6 mol%), NaO^tBu (1.5 eq.), toluene, 100 °C, 20 h, 45%; **b**: ketone **217** (1 eq.), KHMDS (1.1 eq.), THF, 2-[*N,N-bis*(trifluoromethanesulfonyl)amino]-5-chloropyridine **172** (1.1 eq.), 0 °C-rt, 12 h, 89%; **c**: vinyl triflate **218** (1 eq.), $AgNO_3$ (15 eq.), 2,6-lutidine (8 eq.), THF:H_2O (4:1), rt, 1 h, 68%; **d**: thiol **219** (1 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6 mol%), Cs_2CO_3 (1.5 eq.), dioxane, 100 °C, 20 h, 47%;

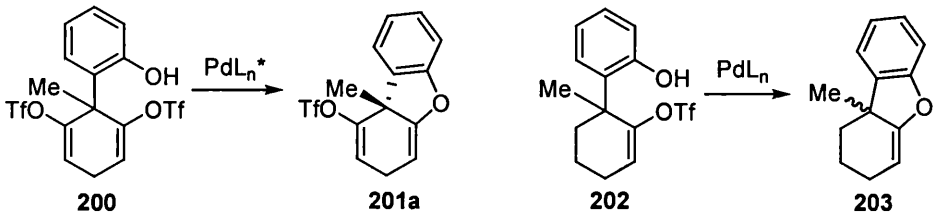
Scheme 5.9 Intramolecular palladium-catalysed aryl thiol cyclisation with vinyl triflates

The palladium-catalysed α-arylation of cyclohexanone with the SEM protected *o*-bromobenzenethiol **216** was successful applying the same catalyst system as the SEM protected *o*-bromophenol [$Pd_2(dba)_3$, $HP^tBu_3BF_4$, NaO^tBu] to give α-arylated cyclohexanone **217** although in a lower yield of 45%. Transformation to the more highly substituted triflate proceeded in an excellent yield (89%) employing identical conditions as the *O*-SEM substrate. However, deprotection of the *S*-SEM group proved problematic and it could not be cleaved employing the milder acid and fluoride conditions previously determined for the deprotection of the *O*-SEM group (*O-O*-ketal). This mixed *O-S*-ketal system required harsher conditions and was efficiently removed

when treated with an aqueous mixture of silver nitrate and 2,6-lutidine[37] in less than one hour giving the free thiol **219** in a 68% yield. Finally, the palladium-catalysed intramolecular cyclisation of the nucleophilic thiol onto the vinyl triflate gave the expected benzothiophene **155** in a moderate yield of 47%.

5.3 Steps towards an enantioselective intramolecular palladium-catalysed synthesis of aryl enol ethers

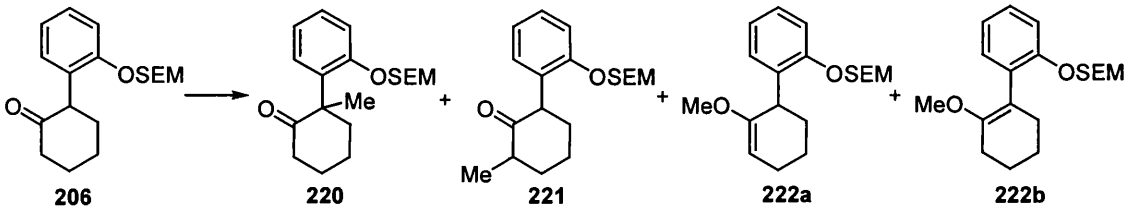
In order to generate an *enantio*-enriched quaternary carbon centre *via* desymmetrisation of a *bis*-vinyl triflate **200** using a chiral palladium catalyst, we first had to prepare a more simplified α,α-substituted mono-triflate **202** from the corresponding mono-ketone. This would help determine whether or not construction of the more highly strained aryl enol ether **201a/203** would be achievable employing an achiral palladium catalyst (**Scheme 5.10**).



200 **201a** **202** **203**

Scheme 5.10 Enantioselective intramolecular palladium-catalysed *C-O* bond formation

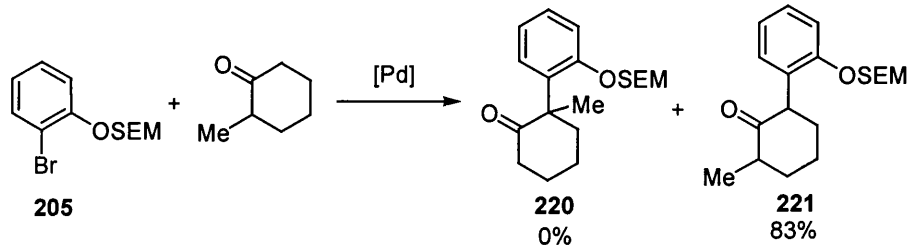
Unfortunately, the synthesis of substrate **202** proved more arduous than anticipated despite the reaction pathway involving only an additional methylation step compared with the previous investigation (**Scheme 5.11**). This reaction, in one-step, involves direct trapping of the thermodynamic enolate **220** with a methylating agent. Several products are possible including methylation at the less hindered α-carbon **221**, or at the oxygen of the enolate **222a/b**. Several methods exist for the methylation of α-phenyl cyclohexanone including a reaction with sodium azide in diethyl ether,[38] indirect alkylation *via* silyl[39-41] and stannyl[42] enol ethers and employment of transition metal catalysts,[42-44] but the most simplified system employs a base for enolisation with subsequent trapping of the enolate with a methylating agent *eg.* MeI, Me_2SO_4 or MeOTf.[45]



Scheme 5.11 Evasive methylation of ketone **206**

Employment of sodium hydride as base with methyl iodide as the methylating reagent in DMF at moderate temperatures up to 50 °C, to ensure the formation of the thermodynamic enolate, gave a mixture of products. Polyalkylation products were evident[46] and subsequent reactions using diethylzinc to suppress this gave fewer products, although none were isolable in pure form. The desired product was isolated in a poor yield of 23%, albeit on a milligram scale. We were, however, unable to reproduce this reactivity. Reducing the temperature to ambient temperature and to -78 °C reduced the number of products, but none of the desired product **220** was synthesised. Manganese bromide has also been shown to be effective at suppressing over alkylation of ketone enolates.[47] Employment of the potassium and lithium bases,[39] KH, KHMDS or ^{n}BuLi at varying temperatures with both methyl iodide and dimethyl sulfate as methylating agents proved ineffective. The generation of the thermodynamic enolate with KH at temperatures of -30 °C to rt and trapping with methyl triflate gave undesired formation of the benzofuran in 30% prior to methylation.[45] It was thought that the production of triflic acid was sufficient to cleave the SEM group and initiate cyclisaiton.

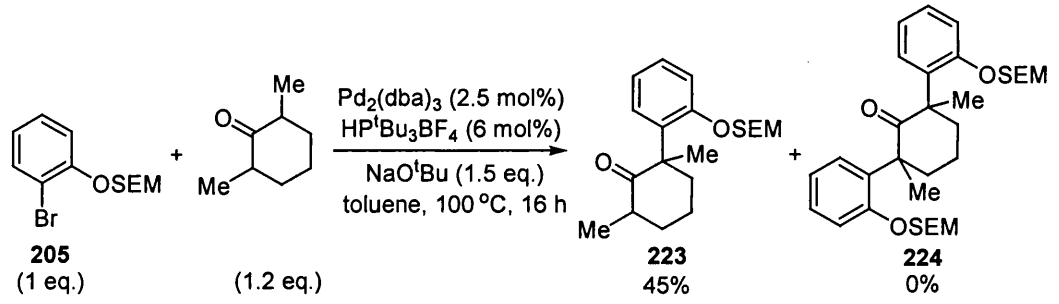
Further investigations into two-step syntheses will be undertaken, however due to time constraints we decided to investigate an alternative approach involving palladium-catalysed α-arylation of 2-methylcyclohexanone to give the α,α-disubstituted ketone **220** (**Scheme 5.12**). As expected, substitution at the less hindered α-carbon gave the α,α'-disubstituted ketone **221** as the only product.



Conditions: ketone (1 eq.), halide **205** (1.2 eq.), $Pd_2(dba)_3$ (2.5 mol%), $HP^tBu_3BF_4$ (6 mol%), NaO^tBu (1.5 eq.), toluene, 100 °C, 16 h.

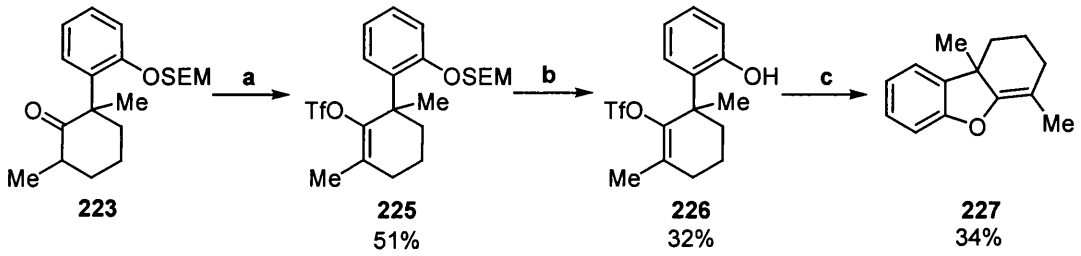
Scheme 5.12 Palladium-catalysed α-arylation of 2-methylcyclohexanone

Employment of the symmetrical 2,6-dimethylcyclohexanone created the desired quaternary centre **223** albeit in a lower yield of 45% (**Scheme 5.13**). No double α-arylation **224** was observed. Only a few examples of palladium-catalysed α-arylation of ketones that formed quaternary carbon centres had been reported in the literature[1] until the group of Buchwald reported a series of α-arylations[48] and α-vinylations[49] of α'-blocked α-alkylcycloalkanones. They chose to install an *N*-methyl-anilinomethylene moiety to block the secondary α-carbon, leaving the tertiary α-carbon centre to be reacted upon. This blocking group could be easily installed in high yield with KO^{t}Bu, ethylformate and *N*-methyl aniline, and easily removed by hydrolysis with aqueous HCl followed by a retro-Claisen reaction of the formylated ketone under basic conditions. In the future this protocol may be applied to our substrate, as removal of the -SEM group requires treatment with aqueous HCl at elevated temperatures and for that reason will not be deprotected prematurely with the blocking group.



Scheme 5.13 Palladium-catalysed α-arylation of 2,6-dimethylcyclohexanone

Scheme 5.14 depicts the un-optimised synthesis of the more highly strained aryl enol ether **227** *via* intramolecular palladium-catalysed *C-O* bond formation between a vinyl triflate and proximal phenol.

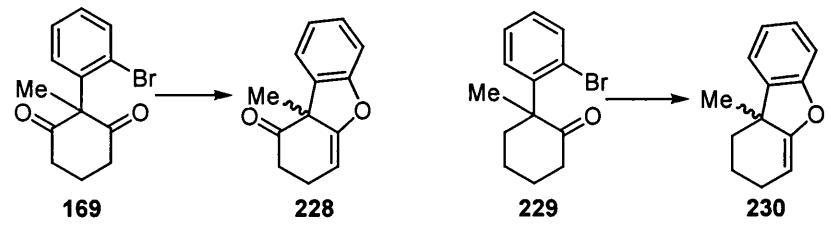


Conditions: **a**: ketone **223** (1 eq.), KHMDS (1.1 eq.), THF, 2-[*N,N-bis*(trifluoromethanesulfonyl)amino]-5-chloropyridine **172** (1.1 eq.), 0 °C-rt, O/N, 51%; **b**: triflate **225** (1 eq.), HCl (1M, 5 eq.), THF, 80 °C, 6 h, 32%; **c**: $Pd_2(dba)_3$ (2.5 mol%), DPEphos (6 mol%), Cs_2CO_3 (1.5 eq.), toluene, 100 °C, 20 h, **227** not isolated.

Scheme 5.14 Synthesis of a more highly strained aryl enol ether

5.4 Extension to *O*-enolate cyclisation methodology

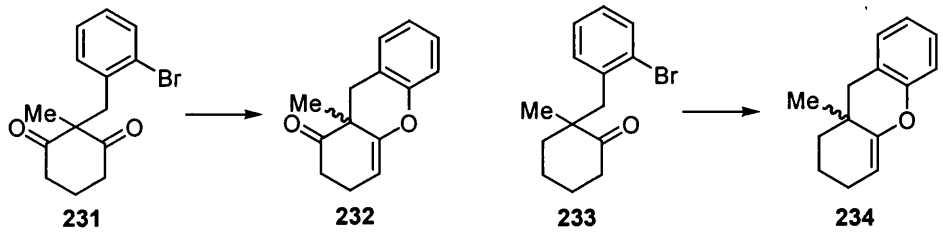
We envisaged the desymmetrisation of the diketone **169** employing our palladium catalysed *O*-enolate cyclisation strategy (**Chapter 3**). However, due to time constraints and the capricious nature of the methylation step required to synthesise the starting ketone **229** this methodology was deferred for the present time (**Scheme 5.15**).



169 **228** **229** **230**

Scheme 5.15 Synthesis of aryl enol ether *via* palladium-catalysed *O*-enolate cyclisation

Instead, we successfully prepared 2-(2-bromobenzyl)-2-methylcyclohexanone **233** as a simpler version of **231** by α-benzylating 2-methylcyclohexanone *via* the thermodynamic enolate, favoured at elevated temperatures of 50 °C and under basic conditions with NaH. The introduction of an equivalent of $ZnEt_2$ minimises polyalkylation side products to give the desired product in a moderate yield of 40% (in the absence of $ZnEt_2$ the polyalkylated product was solely observed in a yield of 50%) (**Scheme 5.16**). Cyclisation of this substrate would give the aryl enol ether adduct **234**, constructing a six-membered ring as opposed to a five-membered ring as previously proposed.

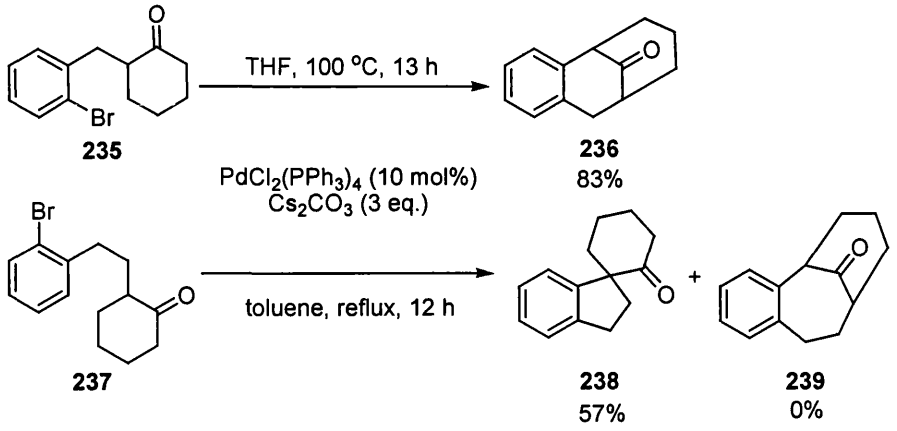


231 **232** **233** **234**

Scheme 5.16 Palladium-catalysed *O*-enolate cyclisation with formation of 6-membered ring

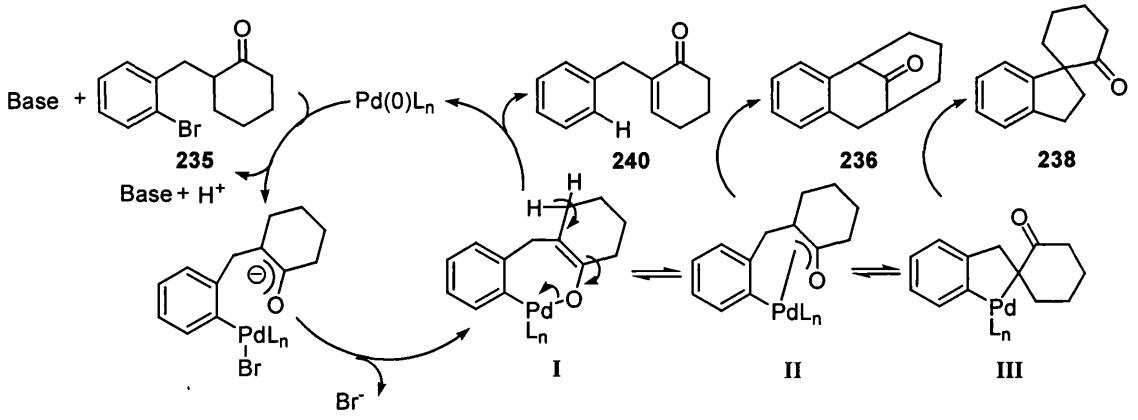
In 1997, Muratake and Natsume reported the palladium catalysed intramolecular α-arylation of 2-(2-bromobenzyl)-cyclohexanone **235** (**Scheme 5.17**).[50,51] This substrate is almost identical to the one we wished to investigate without the additional α-methyl group making it less sterically strained. They recovered the cyclised product **236** in an excellent yield of 83% upon treatment with $PdCl_2(PPh_3)_2$ and Cs_2CO_3 as base in THF at elevated temperatures. The equivalent cyclisation was successfully performed with the

cyclopentanone and cycloheptanone derivatives, although in lower yields. Increasing the tether length between the aryl and ketone unit gave a more flexible backbone **237**, allowing for the formation of a more favourable five membered ring at the tertiary carbon centre to give the spirocyclic product **238**, none of the seven-membered ring was observed **239**.



Scheme 5.17 Intramolecular α-arylation of aliphatic ketones

Hogenauer and Mulzer proposed the catalytic cycle depicted in **Scheme 5.18** to account for an unusual palladium catalysed intramolecular redox reaction. This led to the formation of α,β-unsaturated ketone **240** by treatment of **235** with catalytic amounts of the Hermann-Beller palladacycle[52,53] $Pd_2(\mu_2\text{-}OAc)_2(o\text{-}(P(o\text{-}Tol)_2)CH_2Ph)_2$ and $^nBu_4NOAc$ in DMF at elevated temperatures.[54]

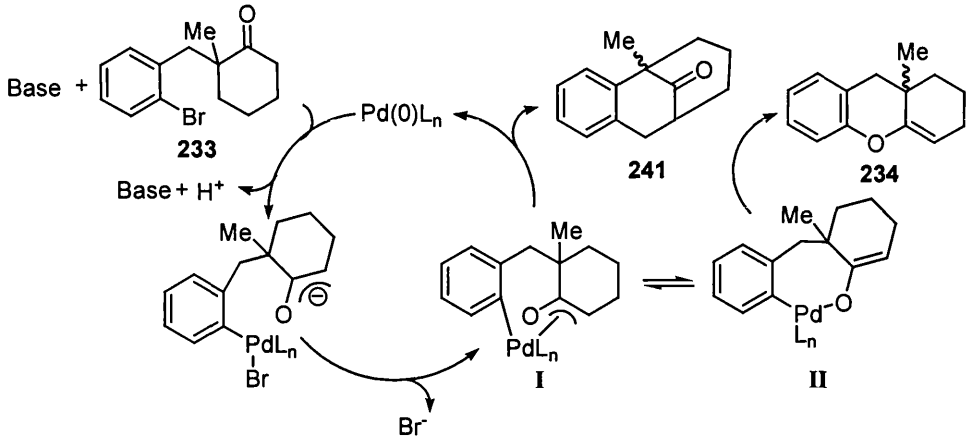


Scheme 5.18 Proposed catalytic cycle for the palladium-catalysed cyclisation of 2-(2-bromobenzyl)-cyclohexanone

The α,α'-disubstituted ketone **236** and the spirocyclic ketone **238** can also be explained *via* reductive elimination from one of three expected organopalladium complexes (**I-III**). Neither of the latter substrates were observed under these conditions, confirming

that a change in catalyst conditions would indeed have an effect on the identity of the final product.

The introduction of a α-methyl group to construct a quaternary carbon centre prevents the ability to α-arylate at that position, forcing the cyclisation to occur *via* the α'-carbon **241** or *via* the oxygen of the enolate **234** (**Scheme 5.19**).

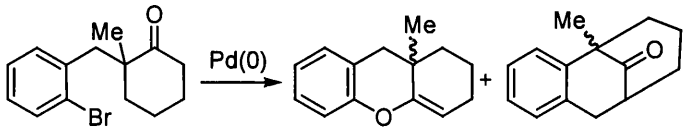


Scheme 5.19 Palladium-catalysed synthesis of strained aryl enol ether

Investigations were undertaken to determine the effect that the counterion has on the electronic distribution across the enolate and whether or not we can influence the enolate geometry in the organopalladium complex (**I** or **II**) to favour the *O*-enolate cyclisation **234** by simply changing the base. A range of bi-dentate and mono-dentate ligands of varying electron donor ability and steric bulk were tested.

Preliminary studies were carried out with our original *O*-enolate cyclisation catalyst, optimised for the formation of the five-membered ring in the benzofuran motif [$Pd_2(dba)_3$, DPEphos, Cs_2CO_3]. Treatment of ketone **233** with this catalyst at 100 °C yielded 73% of the undesired *C*-arylated product **241** (entry 1, **Table 5.1**). Exchanging the base for NaO^tBu and lowering the temperature to 80 °C gave a lower conversion of 20% **241**, but none of the desired *O*-arylated product **234** (entry 2). Unfortunately, employing the stronger NaHMDS base gave 100% conversion to **241** at 80 °C (entry 3). Substitution of the counterion from Na to K gave the desired *O*-arylated product **234** in a 22% isolated yield (entry 4), showing that the counterion had a definite effect on the enolate geometry and substitution. The ability of the counterion to form an ion pair with the oxygen of the enolate decreases in the order Na > K > Cs. Although cesium gives the most nucleophilic or 'naked' *O*-enolate, the base Cs_2CO_3 is very weak and likely to deprotonate the enolate after the formation of the organopalladium intermediate **I** (**Scheme 5.19**), and as the palladium is a 'soft' centre it will interact more strongly with

the carbon centre thus favouring the formation of the *C*-arylated product **241**. On the other hand KHMDS is a strong base thus deprotonation readily occurs to form the enolate with the potassium counterion weakly co-ordinated to the oxygen. This makes it more nucleophilic, favouring the other organopalladium tautomer **II** (**Scheme 5.19**) and *O*-enolate cyclisation. Addition of a crown ether to sequester the potassium ion would render the oxygen atom even more nucleophilic, further increasing the ratio of *O*-arylation to *C*-arylation. However, in practise, only degradation of the starting material was observed (entry 5).



233 **234** **241**

Table 5.1 Optimisation of palladium catalyst parameters[a]

Entry	Ligand	Base	Conv. **234**:**241** (%)
1[b]	DPEphos	Cs_2CO_3	0:73
2	"	NaO^{t}Bu	0:20 + starting ketone
3	"	NaHMDS	0:100
4[c]	"	KHMDS	22:27[d]
5[e]	"	KHMDS + 18-crown-6 (0.3 eq.)	degradation
6[f]	S-phos	Cs_2CO_3 or KHMDS	0:100
7	HP^{t}Bu$_3$BF$_4$	KHMDS	0:41 + starting ketone
8	Xantphos	"	0:40 + starting ketone
9	Dave-phos	"	0:100
10	**3b**	"	0:100
11	**12c**	"	degradation

Conditions: **a**: ketone **233** (1 eq.), $Pd_2(dba)_3$ (2.5 mol%), ligand (6 mol%), toluene, 80 °C; **b**: 100 °C; **c**: temperature gradient rt-100 °C **241** formation at 80 °C; **d**: isolated yield; **e**: alternative additive tried: BEt_3 (1 eq.) 100% **241** and (5 mol%) no products; **f**: X-phos also gave 100% **241**.

Unfortunately, a brief investigation of ligand effects did not lead to the generation of a more effective catalyst system. Surprisingly, use of our alternative catalyst system for the one-pot *O*-enolate cyclisation [$Pd_2(dba)_3$, S-phos] with either Cs_2CO_3 or KHMDS gave the *C*-arylated product **241** in quantitative yield (entry 6). Substituting S-phos for the more highly substituted X-phos gave only **241**. Catalysts generated from the bulky phosphine salt HP^{t}Bu$_3$BF$_4$ and the bidentate ligand Xantphos also resulted in the formation of the *C*-arylated product **241**, although starting material was also recovered indicating sluggish reactivity (entries 7 and 8). Employment of the biphenyl ligands

Dave-phos **4a** and **3b** gave 100% conversion to the *C*-arylated product **241** (entries 9 and 10). Finally, the bidentate di-*tert*-butylphosphino ferrocenyl ligand **12b** that previously showed promise towards the *O*-enolate cyclisation, gave neither of the desired products, but degradation of the starting material (entry 11).

5.5 Concluding Comments

In summary, a high yielding route for the preparation of cyclic aryl enol ethers has been developed *via* an intramolecular palladium catalysed *C-O* bond forming reaction between a phenol and a vinyl triflate. Application of this methodology to the analogous *C-S* bond forming reaction between a thiol and vinyl triflate gave the corresponding benzothiophene in moderate yield. Preliminary studies towards the expansion of our palladium-catalysed *O*-enolate cyclisation system for the formation of six-membered ring aryl enol ethers were successful. This work will be explored further and expanded to incorporate our desymmetrisation strategy.

5.6 References

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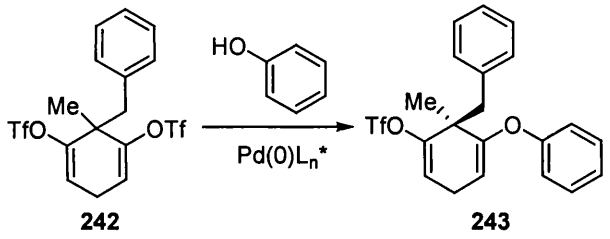
Chapter 6 Summary and Future Work

6.1 Summary

The project presented has shown the development of several new methods for the formation of *C-O* and *C-S* bonds using palladium catalysis. Our initial work observed the formation of a range of aryl enol ether derivatives. These were obtained in up to 98% yield from the cross coupling of vinyl triflates with electron-rich, -neutral and -poor phenols in the presence of the catalyst system [$Pd_2(dba)_3$, di-*tert*-butylphosphinobiphenyl **3b**, NaO^tBu] (**Chapter 2**). An intramolecular variant of this protocol was achieved in quantitative yield in the presence of the modified catalyst system [$Pd_2(dba)_3$, DPEphos, Cs_2CO_3] (**Chapter 5**). The same catalyst combination was found to be effective for the preparation of a number of benzo[*β*]furans *via* an *O*-enolate cyclisation of α-arylated ketones in up to 95% yield (**Chapter 3**). An unusual two-ligand catalyst system realised the synthesis of a simple benzo[*β*]furan from the ketone and 1,2-dihalobenzene starting materials effecting a tandem α-arylation/*O*-enolate cyclisation reaction [$Pd_2(dba)_3$, Xantphos, DPEphos, Cs_2CO_3]. As a result of the availability of new ligands, a catalyst system employing the ligand S-phos proved more efficient in carrying out the two-step, one-pot reaction. Preliminary studies towards variations of tether length of the aryl group and steric hinderance in the α-position of the α-arylated ketone intermediates have shown promise (**Chapter 5**). Development of these methodologies to include the analogous *C-S* bond formations have proven very successful and thus give a more comprehensive series of results worthy of extension to our desymmetrisation protocol.

6.2 Future Work

We first envisage the application and expansion of our already established palladium catalysed intermolecular enol ether formation methodology, (described in **Chapter 2**) to the selective intermolecular palladium catalysed desymmetrisation of *bis*-vinyl triflates **242** to form aryl enol ethers **243** (**Scheme 6.1**).



Scheme 6.1 Intermolecular desymmetrisation of *bis*-vinyl triflate **242**

In order to obtain the best possible enantioselectivities it will be necessary to screen a pool of chiral ligands (**Figure 6.1**) and, as a consequence, it may be necessary to re-optimise the reaction parameters. It is hoped treatment with a chiral palladium catalyst will effect enantioselective *C-O* bond formation, complimenting the *C-C* bond formations already developed.[1]

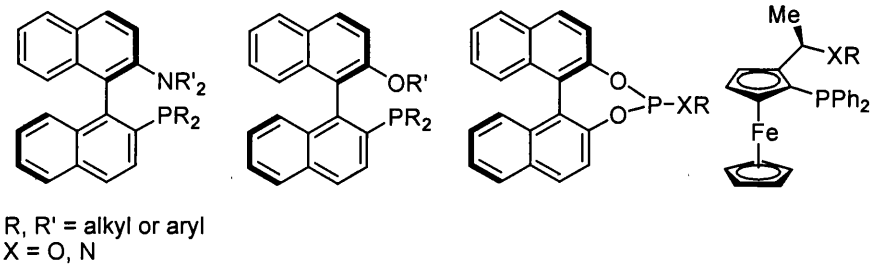
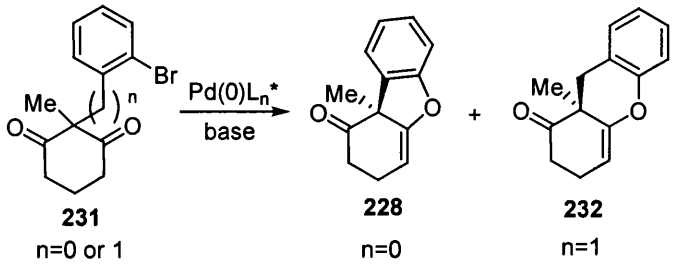


Figure 6.1 Possible chiral ligands for desymmetrisation

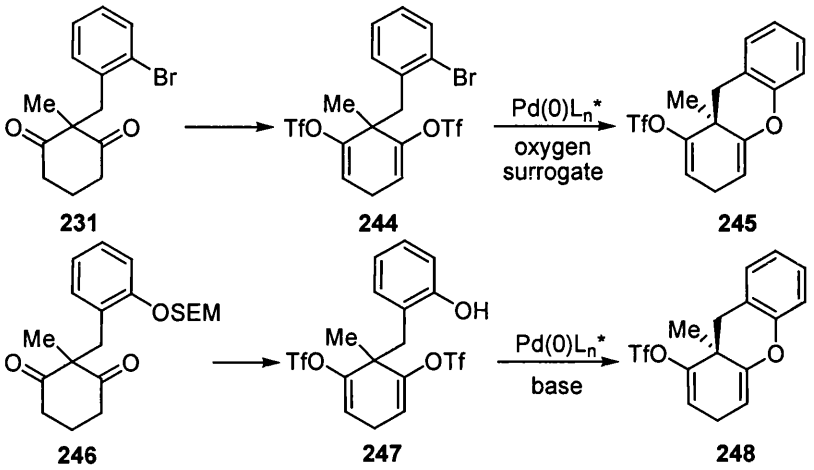
Similarly, we would like to apply and expand our intramolecular palladium catalysed *O*-enolate cyclisation methodology, (described in **Chapter 3**) to the desymmetrisation of diketone **231** to give benzofuran **228** when n=0 or aryl enol ether **232** when n=1 (**Scheme 6.2**). Again, it would be necessary to re-optimise the catalyst system to incorporate a chiral catalyst. It may also be possible to use a chiral base with an achiral ligand to effect the desymmetrisation.



Scheme 6.2 Intramolecular desymmetrisation strategy: palladium catalsed *O*-enolate cyclisation

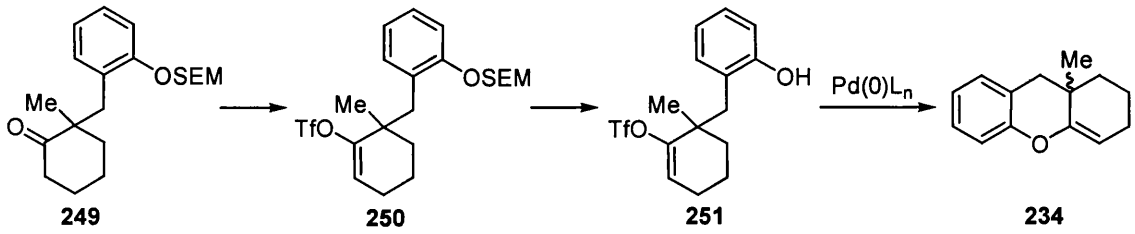
Finally, the preparation of diketones **231** and **246** and their subsequent conversion to *bis*-vinyl triflate substrates **244** and **247** would allow the application of our tandem oxygen surrogate strategy (**Chapter 4**) and intramolecular aryl enol ether protocol

(**Chapter 5**) towards the desymmetrisation of these substrates (**Scheme 6.3**). However, further studies must first be undertaken to improve the oxygen surrogate catalyst system, investigating alternative palladium sources and ligand combinations (see **Chapter 4**).



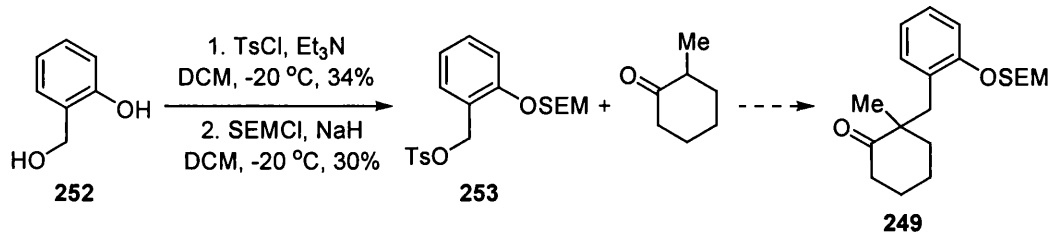
Scheme 6.3 Intramolecular desymmetrisation strategies

The aryl-alkyl substrates can be prepared using palladium-catalysed arylation of the corresponding diketone followed by vinyl triflate formation. Variations of ring size and tether length will be examined to form a range of heterocycles.



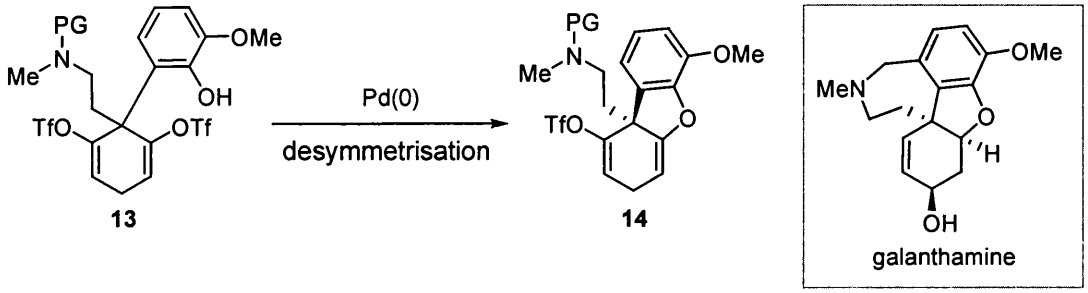
Scheme 6.4 Intramolecular cyclisation to form aryl enol ether **234**

When preliminary studies were embarked upon to determine the feasibility of the cyclisation of the simpler mono-vinyl triflate substrate **249** employing an achiral catalyst (**Scheme 6.4**), a suitable masked phenol had to be prepared that could be employed in the α-alkylation of 2-methylcyclohexanone (**Scheme 6.5**). The attempt to form SEM protected phenol **253** from the commercially available diol **252** involved the protection of the benzylic alcohol prior to the SEM protection of the phenolic oxygen. Unfortunately, both reactions proved sluggish. When general α-alkylation conditions were used (strong base (NaH or ^{n}BuLi) at varying temperatures (-78 °C to 50 °C)) none of the desired product was obtained. Alternative substrates and α-alkylation conditions are being investigated within the Willis laboratory.



Scheme 6.5 Formation of **249** employing α-alkylation

To complete the body of work the aforementioned methodologies would be applied to the total synthesis of galanthamine, an anti-Alzheimer's drug (**Scheme 6.6**). The symmetrical *bis*-vinyl triflate **13** can be readily prepared from a diketone, a protected 2-bromophenol and an activated amine. An intramolecular *etherification* reaction would generate the unsymmetrical aryl enol ether **14**. It is envisaged advancement through a series of known reactions: triflate reduction, enol ether reduction and deprotection would give the desired product.



Scheme 6.6 Desymmetrisation: application towards the part synthesis of galanthamine

6.3 References

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Chapter 7 Experimental

7.1 General Experimental

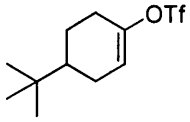
Prior to use, solvents were dried and purified in the following manner: hexane and toluene were distilled under nitrogen from sodium, using benzophenone ketal as an indicator where necessary; dichloromethane and 1,4-dioxane were distilled under nitrogen from calcium hydride. Pre-dried dimethylformamide was purchased from Sigma-Aldrich and used without further purification. All other solvents were dried by an MBraun SPS solvent system. Petrol refers to the fraction of light petroleum, possessing bp 40-60 °C.

Commercially available reagents were used as purchased. Ligands were purchased from Sigma-Aldrich and Strem Chemicals. All experiments were performed under an inert atmosphere of nitrogen (N_2).

^{1}H NMR spectra were recorded from samples in $CDCl_3$ solution at 300 MHz or 400 MHz using BRUKER AM 300 MHz or JEOL EX 400 MHz spectrometers respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (δ_H 0.00) or residual $CHCl_3$ (δ_H 7.26) as an internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz and 100 MHz using BRUKER AM 300 MHz or JEOL EX 400 MHz spectrometers respectively, using $CDCl_3$ (δ_C 77.0) as an internal reference. All *J* couplings are quoted in Hz. IR spectra were recorded in the range 4000-600 cm^{-1} as: liquid films, Nujol mulls or KBr discs, using a Perkin Elmer FT1000 spectrometer. Mass Spectra were recorded at the EPSRC Mass Spectrometry Centre, Swansea. Microanalysis was carried out by the University of Bath analytical service. Thin layer chromatography was carried out using plastic or aluminium-backed plates with Merck Kieselgel 60 GF_{254} coating. Plates were visualised using UV light (254 nm) and/or by staining with potassium permanganate or vanillin followed by heating. Flash chromatography was carried out using Merck 60 H silica gel or Brockmann aluminium oxide, activated, neutral (50-200 microns). Samples were loaded onto the column as either a saturated solution or pre-absorbed onto silica gel or neutral alumina before purification.

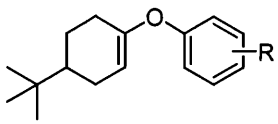
7.2 Experimental Analyses

Preparation of **4-*tert*-butyl-cyclohex-1-enyl trifluoromethanesulfonate, 21**



A solution of trifluoromethanesulfonic anhydride (10.01 g, 0.04 mol, 5.96 mL) in anhydrous DCM (27 mL) was added dropwise over 15 minutes to a suspension of 4-*tert*-butylcyclohexanone (2.78 g, 0.02 mol) and anhydrous sodium carbonate (3.71 g, 0.04 mol) in DCM (27 mL) under nitrogen. The reaction mixture was stirred at room temperature for 24 hours, after which, the reaction was quenched and washed with a saturated aqueous $NaHCO_3$ solution (2 × 100 mL). The combined aqueous washings were extracted with DCM (2 × 100 mL) and the combined organic extracts dried over $MgSO_4$, filtered and reduced *in vacuo*. The product was purified *via* flash column chromatography (2% ethyl acetate:petrol) to yield triflate **21** (3.578 g, 70%) as a pale amber oil. υ_{max} (film)/cm^{-1} 2963, 2883, 1694, 1417, 1247, 1209, 1145, 871; δ_H (300 MHz, $CDCl_3$) 0.90 (9H, s, $C(CH_3)_3$), 1.27-1.42 (2H, m, $CHC(CH_3)_3$ and CH_2CH), 1.88-2.02 (2H, m, CH_2), 2.15-2.42 (3H, m, $CH_2C{=}CH$ and $CH_2CH{=}C$), 5.65 (1H, app. dt, *J* 5.9 and 1.8, C=C*H*); δ_C (75 MHz, $CDCl_3$) 23.7, 25.0, 26.8, 28.2, 31.7, 42.5, 118.1, 148.9; $C_{11}H_{16}O_3SF_3$ requires C 46.14, H 5.98%, found C 46.80, H 5.99%. Data are in agreement with literature values. [1,2]

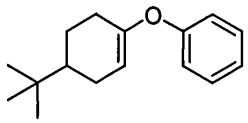
General Procedure A: Preparation of Enol Ethers From Vinyl Triflates by Palladium Catalysis



Sodium *tert*-butoxide (118 mg, 1.22 mmol) was added to a flask charged with $Pd_2(dba)_3$ (19 mg, 0.02 mmol) and *bis-tert*-butylbiphenylphosphine (18 mg, 0.06 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (5 mL) and the required phenol (1.05 mmol) was added prior to the addition of triflate **X** (200 mg, 0.70 mmol). The reaction mixture was heated to 100 °C and allowed to stir for between 19-24 hours, after which, the reaction was cooled to room temperature, diluted with hexane (30 mL), filtered through celite and reduced *in vacuo*. The product was purified by flash column

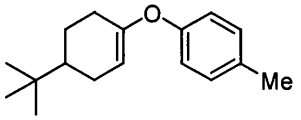
chromatography: neutral alumina; (petrol:ethyl acetate) to yield the products as colourless to amber oils in moderate to excellent yields.

Preparation of **(4-*tert*-butyl-cyclohex-1-enyloxy)-benzene, 64**



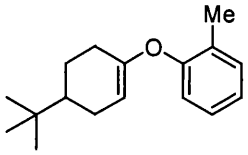
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **X** (200 mg, 0.70 mmol) and phenol (99 mg, 1.05 mmol) gave *enol ether* **64** (136 mg, 85%) as a colourless oil. υ_{max} (NaCl)/cm^{-1} 2295, 1679, 1591, 1483, 1363, 1226, 1150, 750, 700; δ_H (300 MHz, $CDCl_3$) 0.83 (9H, s, C(C*H*$_3$)$_3$), 1.21-1.33 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.79-1.89 (2H, m, C*H*$_2$), 1.95-2.21 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 4.97 (1H, app. dt, *J* 5.8 and 2.7, C=C*H*), 6.86-7.01 (3H, m, Ar-*H*), 7.16-7.28 (2H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 22.4, 23.2, 25.5, 25.6, 25.9, 42.2, 105.2, 116.6, 120.5, 127.4, 156.7, 157.7; *m/z* LRMS (EI$^+$) 230 [M]$^+$ (22%), 173 [M-^{t}Bu]$^+$ (17%), 94 [PhOH] (83%); HRMS (ES$^+$) calc. for $C_{16}H_{22}O$: 230.1671 [M]$^+$; found: 230.1675 [M]$^+$.

Preparation of **1-(4-*tert*-butyl-cyclohex-1-enyloxy)-4-methyl-benzene, 65**



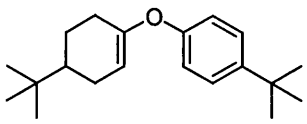
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 4-methylphenol (114 mg, 1.05 mmol) gave *enol ether* **65** (135 mg, 80%) as a pale amber oil. υ_{max} (NaCl)/cm^{-1} 2995, 1678, 1600, 1508, 1367, 1220, 1190; δ_H (300 MHz, $CDCl_3$) 0.81 (9H, s, C(C*H*$_3$)$_3$), 1.15-1.34 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.68-1.89 (2H, m, C*H*$_2$), 2.00-2.18 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 2.24 (3H, s, Ar-C*H*$_3$), 4.87 (1H, app. dt, *J* 5.8 and 2.7, C=C*H*), 6.80 (2H, d, *J* 7.9, Ar-*H*), 7.02 (2H, d, *J* 7.9, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.4, 26.8, 27.8, 28.2, 44.4, 54.1, 105.8, 119.2, 130.1, 138.0, 146.6, 148.0; *m/z* LRMS (CI$^+$, NH_3) 245 [M+H]$^+$, 229 [M-Me]$^+$, 187 [M-^{t}Bu]$^+$, 172 [M-C_5H_{12}]$^+$, 154 [$C_{10}H_{18}O$], 108 [MePhOH]; HRMS (ES$^+$) calc. for $C_{17}H_{25}O$: 245.1900 [M+H]$^+$; found: 245.1894 [M+H]$^+$.

Preparation of **1-(4-tert-butyl-cyclohex-1-enyloxy)-2-methyl-benzene, 66**



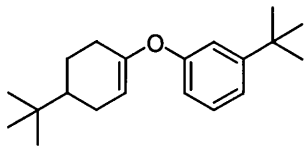
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 2-methylphenol (114 mg, 1.05 mmol) gave *enol ether* **66** (65 mg, 20%) as a colourless oil. υ_{max} (NaCl)/cm^{-1} 3020, 2970 (br), 1679, 1586, 1480, 1471, 1364, 1290, 1250, 1200, 1125, 810, 760, 750; δ_H (300 MHz, $CDCl_3$) 0.82 (9H, s, C(C*H*$_3$)$_3$), 1.03-1.27 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.48 (3H, s, Ar-C*H*$_3$), 1.66-2.02 (2H, m, C*H*$_2$), 2.08-2.27 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 4.62 (1H, app. dt, *J* 5.9 and 2.4, C=C*H*), 6.86 (1H, d, *J* 8.6, Ar-*H*), 6.92 (1H, t, *J* 7.9, Ar-*H*), 7.03-7.15 (2H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 16.5, 24.6, 25.3, 27.8, 28.3, 32.6, 44.5, 103.3, 119.7, 123.4, 126.9, 129.9, 131.2, 153.6, 154.1; *m/z* LRMS (CI$^+$, NH_3) 263 [M+NH$_4$]$^+$, 246 [M+H]$^+$ 245 [M]$^+$, 187 [M-^{t}Bu]$^+$; HRMS (ES$^+$) calc. for $C_{17}H_{25}O$: 245.1900 [M+H]$^+$; found: 245.1899 [M+H]$^+$.

Preparation of **1-*tert*-butyl-4-(4-*tert*-butyl-cyclohex-1-enyloxy)-benzene, 67**



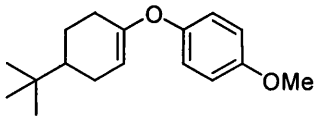
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 4-*tert*-butylphenol (158 mg, 1.05 mmol) gave *enol ether* **67** (201 mg, 100%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 3075, 2900 (br), 1678, 1602, 1508, 1467, 1361, 1302, 1232, 1220, 1100, 1080, 1010, 850, 810; δ_H (300 MHz, $CDCl_3$) 0.82 (9H, s, C(C*H*$_3$)$_3$), 0.97-1.16 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.23 (9H, s, Ar-C(C*H*$_3$)$_3$), 1.65-1.90 (2H, m, C*H*$_2$), 1.91-2.28 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 4.93 (1H, app. dt, *J* 5.4 and 2.7, C=C*H*), 6.83 (2H, d, *J* 8.6, Ar-*H*), 7.23 (2H, d, *J* 8.6, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.5, 25.3, 27.7, 28.0, 31.8, 32.5, 34.5, 44.3, 106.5, 118.2, 126.2, 145.2, 153.1, 153.9; *m/z* LRMS (ES$^+$) 286 [M]$^+$ (5%), 229 [M-^{t}Bu]$^+$ (3%), 150 [^{t}BuPhOH] (26%), 135 [^{t}BuPh] (51%); HRMS (ES$^+$) calc. for $C_{20}H_{31}O$: 287.2361 [M+H]$^+$; found: 287.2369 [M+H]$^+$.

Preparation of **1-*tert*-butyl-3-(4-*tert*-butyl-cyclohex-1-enyloxy)-benzene, 68**



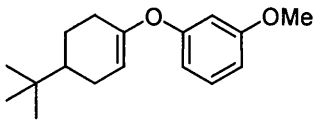
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 3-*tert*-butylphenol (158 mg, 1.05 mmol) gave *enol ether* **63** (100 mg, 80%) as a pale amber oil. υ_{max} (NaCl)/cm^{-1} 3030, 2900 (br), 1678, 1603, 1582, 1486, 1434, 1384, 1271, 1200, 1165, 1100, 900, 790, 700; δ_H (300 MHz, $CDCl_3$) 0.84 (9H, s, C(C*H*$_3$)$_3$), 1.25 (9H, s, Ar-C(C*H*$_3$)$_3$), 1.35-1.36 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.73-1.93 (2H, m, C*H*$_2$), 1.94-2.09 (1H, m, C*H*$_2$C=CH), 2.10-2.28 (2H, m, C*H*$_2$CH=C), 4.95 (1H, app. dt, *J* 5.7 and 2.4, C=C*H*), 6.73 (1H, ddd, *J* 7.9 and 2.4 and 1.3, Ar-*H*), 6.95 (1H, t, *J* 2.3, Ar-*H*), 7.00 (1H, ddd, *J* 7.9 and 2.4 and 1.2, Ar-*H*), 7.16 (1H, t, *J* 7.9, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.7, 25.5, 27.9, 28.2, 31.8, 32.7, 35.2, 44.5, 106.6, 115.5, 116.5, 119.7, 120.7, 128.9, 153.0, 156.1; *m/z* LRMS (CI$^+$, NH_3) 287 [M+H]$^+$, 271 [M-Me]$^+$, 229 [M-^{t}Bu]$^+$, 154 [$C_{10}H_{18}O$], 135 [^{t}BuPh]; HRMS (ES$^+$) calc. for $C_{20}H_{31}O$: 287.2369 [M+H]$^+$; found: 287.2366 [M+H]$^+$.

Preparation of **1-(4-*tert*-butyl-cyclohex-1-enyloxy)-4-methoxy-benzene, 69**



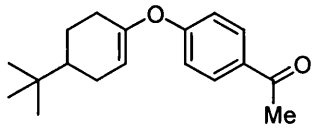
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 4-methoxyphenol (130 mg, 1.05 mmol) gave *enol ether* **69** (72 mg, 40%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 2850 (br), 1679, 1601, 1584, 1507, 1467, 1380, 1367, 1296, 1250, 1200, 1160, 1030, 1125, 850, 790; δ_H (300 MHz, $CDCl_3$) 0.89 (9H, s, C(C*H*$_3$)$_3$), 1.21-1.38 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.78-1.99 (2H, m, C*H*$_2$), 2.01-2.30 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 3.79 (3H, s, OC*H*$_3$), 4.79 (1H, app. dt, *J* 5.9 and 2.7, C=C*H*), 6.82 (2H, app. d, *J* 7.9, Ar-*H*), 6.95 (2H, app. d, *J* 7.9, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.3, 27.8, 28.3, 32.6, 44.5, 56.0, 103.8, 114.7, 121.0, 149.6, 154.6, 155.5; *m/z* LRMS (EI$^+$) 260 [M]$^+$ (12%), 203 [M-^{t}Bu]$^+$ (3%), 124 [MeOPhOH] (74%), 109 [PhO_2H] (18%); HRMS (EI$^+$) calc. for $C_{17}H_{24}O_2$: 260.1771 [M]$^+$; found: 260.1770 [M]$^+$.

Preparation of **1-(4-*tert*-butyl-cyclohex-1-enyloxy)-3-methoxy-benzene, 70**



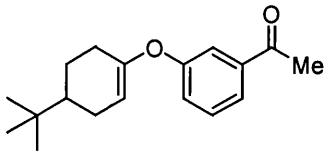
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 3-methoxyphenol (136 mg, 1.05 mmol, 0.12 mL) gave *enol ether* **70** (66 mg, 37%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 2970, 2875, 2350, 1680, 1603, 1488, 1364, 1263, 1180, 1125, 1040, 940, 860, 770; δ_H (300 MHz, $CDCl_3$) 0.83 (9H, s, C(C*H*$_3$)$_3$), 1.00-1.15 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.70-1.90 (2H, m, C*H*$_2$), 1.95-2.27 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 3.72 (3H, s, OC*H*$_3$), 5.04 (1H, app. dt, *J* 5.9 and 2.3, C=C*H*), 6.47 (1H, t, *J* 2.3, Ar-*H*), 6.51 (2H, app. dd, *J* 8.4 and 2.3, Ar-*H*), 7.12 (1H, t, *J* 8.4, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.4, 27.8, 31.9, 32.6, 44.4, 55.7, 104.7, 108.1, 108.3, 110.9, 130.0, 157.0, 159.0, 163.0; *m/z* LRMS (CI$^+$, NH_3) 261 [M+H]$^+$; (EI$^+$) 261 [M+H]$^+$ (3%), 260 [M]$^+$ (26%), 203 [M-^{t}Bu]$^+$ (4%), 124 [MeOPhOH] (83%); HRMS (ES$^+$) calc. for $C_{17}H_{25}O_2$: 261.1849 [M+H]$^+$; found: 261.1848 [M+H]$^+$.

Preparation of **1-[4-(4-*tert*-butyl-cyclohex-1-enyloxy)-phenyl]-ethanone, 71**



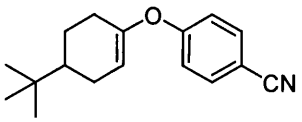
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 4-hydroxyacetophenone (143 mg, 1.05 mmol) gave *enol ether* **71** (80 mg, 42%) as a yellow oil. υ_{max} (NaCl)/cm^{-1} 2900 (br), 1681, 1599, 1503, 1471, 1417, 1385, 1301, 1267, 1241, 1164, 1127, 940, 850, 820; δ_H (300 MHz, $CDCl_3$) 0.85 (9H, s, C(C*H*$_3$)$_3$), 1.16-1.41 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.71-1.93 (2H, m, C*H*$_2$), 1.96-2.30 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 2.49 (3H, s, COC*H*$_3$), 5.22 (1H, app. dt, *J* 5.8 and 2.3, C=C*H*), 6.93 (2H, d, *J* 8.8, Ar-*H*), 7.86 (2H, d, *J* 8.8, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.6, 26.9, 27.7, 27.8, 32.7, 44.3, 111.4, 117.0, 117.1, 130.6, 131.4, 151.4, 161.2, 196.0; *m/z* LRMS (CI$^+$, NH_3) 290 [M+NH$_4$]$^+$, 273 [M+H]$^+$, 219 [$C_{14}H_{18}O_2$], 216 [M-^{t}Bu]$^+$, 173 [M-$C_6H_{12}O$]$^+$, 154 [$C_{10}H_{18}O$], 137 [Me-CO-PhOH]; HRMS (EI) calc. for $C_{18}H_{24}O_2$: 272.1771 [M]$^+$; found: 272.1768 [M]$^+$.

Preparation of **1-[3-4-*tert*-butyl-cyclohex-1-enyloxy)-phenyl]-ethanone, 72**



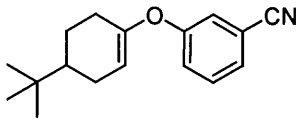
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 3-hydroxyacetophenone (99 mg, 1.05 mmol) gave *enol ether* **72** (113 mg, 60%) as a yellow oil. υ_{max} (NaCl)/cm^{-1} 2950 (br), 1688, 1582, 1481, 1437, 1365, 1355, 1260, 1202, 1175, 1127, 890, 800, 690; δ_H (300 MHz, $CDCl_3$) 0.83 (9H, s, C(C*H*$_3$)$_3$), 1.22-1.40 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.72-1.91 (2H, m, C*H*$_2$), 1.94-2.26 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 2.52 (3H, s, COC*H*$_3$), 4.99 (1H, app. dt, *J* 5.9 and 2.1, C=C*H*), 7.12 (1H, ddd, *J* 7.9 and 2.2 and 1.3, Ar-*H*), 7.32 (1H, t, *J* 7.9, Ar-*H*), 7.48 (1H, m, Ar-*H*), 7.55 (1H, d, *J* 7.9, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.5, 27.7, 27.9, 28.0, 32.7, 44.4, 108.2, 118.2, 122.7, 123.5, 129.7, 138.7, 152.7, 156.8, 196.0; *m/z* LRMS (CI$^+$, NH_3) 290 $[M+NH_4]^+$, 273 $[M+H]^+$; (EI$^+$) 272 $[M]^+$ (12%), 215 $[M-^tBu]^+$ (13%), 188 $[M-^tBu-CO]^+$ (7%), 173 [M-^{t}Bu-COMe] (30%), 136 [MeCOPhOH] (50%); HRMS (ES$^+$) calc. for $C_{18}H_{25}O_2$: 273.1849 $[M+H]^+$; found: 273.1851 $[M+H]^+$.

Preparation of **4-(4-*tert*-butyl-cyclohex-1-enyloxy)-benzonitrile, 73**



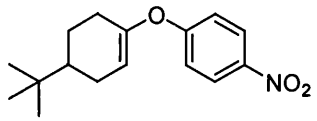
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 4-hydroxybenzonitrile (125 mg, 1.05 mmol) gave *enol ether* **73** (80 mg, 45%) as a yellow oil. υ_{max} (NaCl)/cm^{-1} 2900 (br), 2221, 1904, 1687, 1602, 1503, 1364, 1250, 1110, 1030, 910, 850; δ_H (300 MHz, $CDCl_3$) 0.85 (9H, s, C(C*H*$_3$)$_3$), 1.22-1.39 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.75-1.93 (2H, m, C*H*$_2$), 1.99-2.25 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 5.25 (1H, app. dt, *J* 5.9 and 2.3, C=C*H*), 6.94 (2H, app. d, *J* 8.8, Ar-*H*), 7.51 (2H, app. d, *J* 8.8, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.6, 27.8, 30.2, 32.7, 44.2, 95.0, 112.5, 117.8, 119.3, 134.0, 149.1, 160.7; *m/z* LRMS (CI$^+$, NH_3) 273 $[M+NH_4]^+$, 256 $[M+H]^+$, 255 $[M]^+$, 198 $[M-^tBu]^+$, 171 $[M-^tBu-CN]^+$, 137 $[C_{10}H_{17}]$; HRMS (ES$^+$) calc. for $C_{17}H_{22}NO$: 256.1696 $[M+H]^+$; found: 256.1697 $[M+H]^+$.

Preparation of **3-(4-*tert*-butyl-cyclohex-1-enyloxy)-benzonitrile, 74**



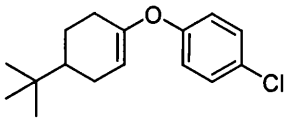
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 3-cyanophenol (125 mg, 1.05 mmol) gave *enol ether* **74** (70 mg, 40%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 2900 (br), 2231, 1689, 1579, 1481, 1430, 1365, 1319, 1254, 1146, 1119, 770, 640; δ_H (300 MHz, $CDCl_3$) 0.84 (9H, s, C(C*H*$_3$)$_3$), 1.17-1.41 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.71-1.92 (2H, m, C*H*$_2$), 1.97-2.22 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 5.12 (1H, app. dt, *J* 5.9 and 2.7, C=C*H*), 7.10-7.35 (4H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.5, 25.4, 27.7, 27.8, 32.6, 44.2, 110.7, 113.4, 118.8, 121.1, 123.1, 126.0, 130.6, 151.9, 157.2; *m/z* LRMS (CI$^+$, NH_3) 273 [M+NH$_4$]$^+$, 256 [M+H]$^+$, 255 [M]$^+$, 198 [M-^{t}Bu]$^+$; HRMS (ES$^+$) calc. for $C_{17}H_{25}N_2O$: 273.1961 [M+NH$_4$]$^+$; found: 273.1962 [M+NH$_4$]$^+$.

Preparation of **1-(4-*tert*-butyl-cyclohex-1-enyloxy)-4-nitrobenzene, 75**



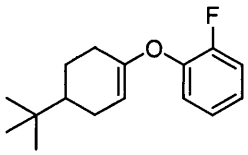
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 4-nitrophenol (146 mg, 1.05 mmol) gave *enol ether* **75** (115 mg, 60%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 2900 br, 1690, 1600, 1590, 1514, 1490, 1394, 1365, 1342, 1250, 1110, 870, 850, 750; δ_H (300 MHz, $CDCl_3$) 0.85 (9H, s, C(C*H*$_3$)$_3$), 1.21-1.41 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.77-1.97 (2H, m, C*H*$_2$), 1.98-2.24 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 5.31 (1H, app. dt, *J* 5.8 and 2.7, C=C*H*), 6.96 (2H, d, *J* 9.8, Ar-*H*), 8.12 (2H, d, *J* 9.8, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.6, 27.8, 28.5, 32.7, 44.2, 113.1, 116.9, 126.0, 151.0, 152.0, 162.5; *m/z* LRMS (CI$^+$, NH_3) 293 [M+NH$_4$]$^+$, 276 [M+H]$^+$, 260 [M-O]$^+$, 246 [M-NO], 230 [M-NO$_2$], 172 [M-^{t}Bu-NO$_2$], 154 [$C_{10}H_{18}O$]; HRMS (ES$^+$) calc. for $C_{16}H_{25}N_2O_3$: 293.1860 [M+NH$_4$]$^+$; found: 293.1860 [M+NH$_4$]$^+$.

Preparation of **1-(4-*tert*-butyl-cyclohex-1-enyloxy)-4-chlorobenzene, 76**



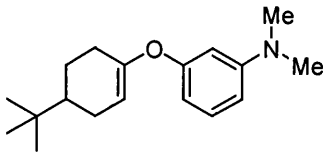
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 4-chlorophenol (135 mg, 1.05 mmol) gave *enol ether* **76** (94 mg, 50%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 1680, 1268, 1125; δ_H (300 MHz, $CDCl_3$) 0.84 (9H, s, C(C*H*$_3$)$_3$), 1.15-1.34 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.72-1.89 (2H, m, C*H*$_2$), 1.95-2.26 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 4.98 (1H, app. dt, *J* 5.8 and 2.7, C=C*H*), 6.85 (2H, app. d, *J* 7.9, Ar-*H*), 7.20 (2H, app. d, *J* 7.9, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.5, 27.8, 28.0, 31.9, 44.4, 107.7, 120.0, 129.5, 134.5, 152.0, 158.0; *m/z* LRMS (CI$^+$, NH_3) 267 [M+H:^{37}Cl]$^+$, 265 [M+H:^{35}Cl]$^+$; (EI$^+$) 266 [M:^{37}Cl]$^+$ (6%), 264 [M:^{35}Cl]$^+$ (18%), 209 [M-^{t}Bu:^{37}Cl]$^+$ (15%), 207 [M-^{t}Bu:^{35}Cl]$^+$ (14%), 182 [$C_{10}H_9ClO$: ^{37}Cl] (17%), 180 [$C_{10}H_9ClO$:^{35}Cl], 130 [PhOHCl:^{37}Cl] (27%), 128 [PhOHCl:^{35}Cl] (100%); HRMS (EI) calc. for $C_{16}H_{21}ClO$: 264.1275 [M:^{35}Cl]$^+$; found: 264.1278 [M:^{35}Cl]$^+$.

Preparation of **1-(4-*tert*-butyl-cyclohex-1-enyloxy)-2-fluorobenzene, 77**



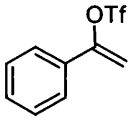
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 2-fluorophenol (118 mg, 1.05 mmol) gave *enol ether* **77** (122 mg, 70%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 2950, 2800, 1683, 1608, 1594, 1500, 1456, 1394, 1379, 1365, 1260, 1190, 1175, 1160, 1120, 870, 810; δ_H (300 MHz, $CDCl_3$) 0.81 (9H, s, C(C*H*$_3$)$_3$), 1.19-1.39 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.64-1.90 (2H, m, C*H*$_2$), 1.92-2.33 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 4.75 (1H, app. dt, *J* 5.9 and 2.3, C=C*H*), 6.91-7.10 (4H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.3, 27.9, 28.2, 32.7, 44.4, 104.0, 116.8 (d, J_{CF} 18.0), 122.1, 124.2 (d, J_{CF} 7.1), 124.4 (d, J_{CF} 3.9), 147.0, 153.7, 155.5; *m/z* LRMS (CI$^+$, NH_3) 249 [M+H]$^+$; (EI$^+$) 249 [M+H]$^+$ (30%), 248 [M]$^+$ (76%), 191 [M-^{t}Bu]$^+$ (56%), 112 [PhOHF] (89%), 95 [PhF] (54%), 93 [PhOH] (66%); HRMS (ES$^+$) calc. for $C_{16}H_{22}FO$: 249.1649 [M+H]$^+$; found: 249.1652 [M+H]$^+$.

Preparation of **[3-(4-*tert*-butyl-cyclohex-1-enyloxy)-phenyl]-dimethylamine, 78**



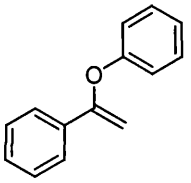
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **21** (200 mg, 0.70 mmol) and 3-(dimethylamino)phenol (144 mg, 1.05 mmol) gave *enol ether* **78** (875 mg, 45%) as an amber oil. υ_{max} (NaCl)/cm^{-1} 2950, 2850, 2815, 1679, 1609, 1575, 1499, 1449, 1364, 1232, 1148, 1000, 840, 760, 700; δ_H (300 MHz, $CDCl_3$) 0.82 (9H, s, C(C*H*$_3$)$_3$), 1.15-1.33 (2H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$CH), 1.71-1.92 (2H, m, C*H*$_2$), 1.94-2.33 (3H, m, C*H*$_2$C=CH and C*H*$_2$CH=C), 2.86 (6H, s, N(C*H*$_3$)$_2$), 4.99 (1H, app. dt, *J* 5.9 and 2.7, C=C*H*), 6.25-6.32 (2H, m, Ar-*H*), 6.38 (1H, d, *J* 8.3, Ar-*H*), 7.07 (1H, t, *J* 8.3, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.4, 27.8, 28.1, 32.6, 41.0, 44.4, 103.6, 106.7, 106.8, 107.3, 129.7, 142.5, 152.5, 157.5; *m/z* LRMS (CI$^+$, NH_3) 299 $[M+NH_4]^+$, 274 $[M+H]^+$, 216 $[M-^tBu]^+$, 154 $[C_{10}H_{18}O]$, 137 $[Me_2NPhOH]$; HRMS (EI) calc. for $C_{18}H_{27}NO$: 273.2087 $[M]^+$; found: 273.2086 $[M]^+$.

Preparation of **1-(1-phenyl)-ethenyloxy-trifluoromethanesulfonate, 80a**



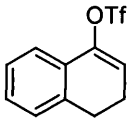
A solution of trifluoromethanesulfonic anhydride (5.09 g, 0.03 mol, 3.03 mL) in anhydrous DCM (15 mL) was added dropwise over 15 minutes to a suspension of acetophenone (1.08 g, 0.01 mol, 1.05 mL) and anhydrous sodium carbonate (1.91 g, 0.02 mol) in DCM (15 mL) under nitrogen. The reaction mixture was stirred at room temperature for 24 hours, after which, the reaction was quenched and washed with a saturated aqueous $NaHCO_3$ solution (2 × 100 mL). The combined aqueous washings were extracted with DCM (2 × 100 mL) and the combined organic extracts dried over $MgSO_4$, filtered and reduced *in vacuo*. The product was purified *via* flash column chromatography (1% diethyl ether: petrol) to yield triflate **80a** (1.20 g, 53%) as a pale green oil. δ_H (300 MHz, $CDCl_3$) 5.29 (1H, d, *J* 4.2, C=C*H*), 5.52 (1H, d, *J* 4.2, C=C*H*), 7.29-7.37 (3H, m, Ar-*H*), 7.46 (2H, dd, *J* 7.4 and 4.1, Ar-*H*). Data are in agreement with literature values.[3]

Preparation of **1-phenyl-1-ethenyloxybenzene, 80b**



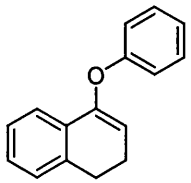
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **80a** (200 mg, 0.70 mmol) and phenol (99 mg, 1.05 mmol) gave enol ether **80b** (95% conv.). The product was very unstable and therefore difficult to purify by flash column chromatography. Crude analysis: δ_H (300 MHz, $CDCl_3$) 4.39 (1H, d, *J* 2.6, C=C*H*), 5.00 (1H, d, *J* 2.6, C=C*H*), 6.69-7.67 (10H, m, Ar-*H*). Data are in agreement with literature values.[4]

Preparation of **3,4-dihydro-naphthalene-1-yl trifluoromethanesulfonate, 81a**



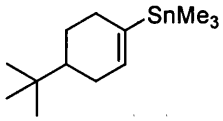
A solution of trifluoromethanesulfonic anhydride (5.09 g, 0.02 mol, 3.03 mL) in anhydrous DCM (15 mL) was added dropwise over 15 minutes to a suspension of α-tetralone (1.32 g, 0.01 mol, 1.20 mL) and anhydrous sodium carbonate (1.91 g, 0.02 mol) in DCM (15 mL) under nitrogen. The reaction mixture was stirred at room temperature for 24 hours, after which, the reaction was quenched and washed with a saturated aqueous $NaHCO_3$ solution (2 × 100 mL). The combined aqueous washings were extracted with DCM (2 × 100 mL) and the combined organic extracts dried over $MgSO_4$, filtered and reduced *in vacuo*. The product was purified *via* flash column chromatography (petrol) to yield triflate **81a** (2.20 g, 88%) as a green oil. δ_H (300 MHz, $CDCl_3$) 2.45 (2H, td, *J* 7.9 and 5.4, CH_2CH=C), 2.81 (2H, t, *J* 7.9, Ar-CH_2), 5.95 (1H, app. t, *J* 5.4, C=C*H*), 7.07-7.14 (1H, m, Ar-*H*), 7.16-7.24 (2H, m, Ar-*H*), 7.25-7.32 (1H, m, Ar-*H*). Data are in agreement with literature values.[5,6]

Preparation of **1-Phenoxy-(3,4-dihydronaphthalene), 81b**



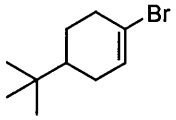
Following the conditions as described in **general procedure A**, the palladium catalysed coupling between triflate **81a** (195 mg, 0.70 mmol) and phenol (99 mg, 1.05 mmol) gave enol ether **81b** (78% conv.). The product was very unstable and therefore difficult to purify by flash column chromatography. Crude analysis: δ_H (300 MHz, $CDCl_3$) 2.33 (2H, td, *J* 7.8 and 5.4, C*H*$_2$CH=C), 2.91 (2H, app. t, *J* 7.8, Ar-*CH*$_2$), 5.30 (1H, app. t, *J* 5.4, C=C*H*), 6.40-7.86 (9H, m, Ar-*H*). Data are in agreement with literature values.[7]

Preparation of **(4-*tert*-butyl-cyclohex-1-enyl)-trimethylstannane, 82**



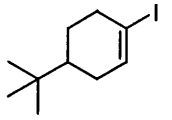
Hexamethylditin (2.00 g, 6.11 mmol) and $Pd(PPh_3)_4$ (0.32 g, 0.27 mmol) were added to a solution of triflate **X** (1.57 g, 5.50 mmol) in anhydrous THF (60 mL) under nitrogen. The lithium chloride (1.39 g, 0.03 mol) was then added and the reaction mixture heated to reflux for 20 hours (the flask was covered in foil to avoid irradiation by light). After cooling, the reaction mixture was diluted with petrol (*ca.* 50 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 mL). The organic extracts were dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified *via* flash column chromatography (petrol) to yield *vinyl stannane* **82** (0.90 g, 54%) as a colourless oil. δ_H (300MHz, $CDCl_3$) 0.64 (18H, s, Sn(C*H*$_3$)$_3$ and C(C*H*$_3$)$_3$), 0.79-1.16 (4H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$), 1.47-1.64 (2H, m, C*H*$_2$ and C*H*$_2$CH=C), 1.66-1.96 (1H, m, C*H*$_2$CH=C), 5.48 (1H, app. s, C=C*H*); δ_C (100 MHz, $CDCl_3$) –9.9, 25.3, 27.5, 29.6, 32.7, 33.0, 44.4, 128.6, 132.2.[8,9]

Preparation of **(4-*tert*-butyl-1-bromo)-cyclohexene, 82a**



A solution of bromine (0.44 g, 2.79 mmol, 0.14 mL) in anhydrous DCM (6 mL) was added dropwise to a solution of vinyl stannane **82** (800 mg, 2.66 mmol) in anhydrous DCM (6 mL) at -78 °C under nitrogen. The reaction mixture was stirred at -78°C for 1 hour before warming to room temperature and reducing *in vacuo*. The crude product was purified by flash column chromatography (petrol) to give vinyl bromide **82a** (460 mg, 80%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 0.82 (9H, s, $C(CH_3)_3$), 1.49-1.67 (2H, m, $CHC(CH_3)_3$ and CH_2), 1.66-1.84 (1H, m, CH_2), 1.96-2.15 (2H, m, CH_2), 2.26-2.40 (1H, m, CH_2), 2.42-2.54 (1H, m, $CH_2CH=C$), 2.70-2.84 (1H, m, $CH_2CH=C$), 4.89 (1H, dd, *J* 5.8 and 2.7, $C=CH$). Data are in agreement with literature values.[10,11]

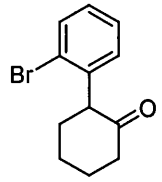
Preparation of **(4-*tert*-butyl-1-iodo)-cyclohexene, 82b**



A solution of iodine (267 mg, 1.05 mmol) in dry DCM (3 mL) was added dropwise to a solution of vinyl stannane **82** (300 mg, 0.10 mmol) in anhydrous DCM (3 mL) at -78 °C under nitrogen. The reaction mixture was stirred at -78 °C for 1 hour before warming to room temperature and reducing *in vacuo*. The crude product was purified by flash column chromatography (petrol) to give vinyl iodide **82b** (150 mg, 57%) as a colourless oil. δ_H (300MHz, $CDCl_3$) 0.86 (9H, s, $C(CH_3)_3$), 1.35-1.50 (2H, m, $CHC(CH_3)_3$ and CH_2), 1.63-2.18 (4H, m, CH_2 and $CH_2CH=C$), 2.45-2.64 (1H, m, $CH_2CH=C$), 6.28-6.34 (1H, m, $C=CH$); *m/z* HRMS (EI+) calc. for $C_{10}H_{17}I$: 264.0369 $[M]^+$; found: 264.0370 $[M]^+$. Data are in agreement with literature values.[12]

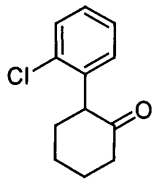
General Procedure B: Preparation of α-Arylated Ketones by Palladium Catalysis

Preparation of **2-(2-bromophenyl)-cyclohexanone, 111**



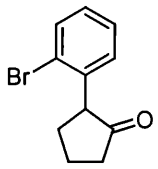
Cesium carbonate (4.57 g, 14.00 mmol) was added to a flask charged with $Pd_2(dba)_3$ (0.03 g, 0.03 mmol) and Xantphos (0.04 g, 0.08 mmol) under nitrogen. The reagents were suspended in anhydrous dioxane (6.35 mL) and 1-bromo-2-iodobenzene (1.80 g, 6.37 mmol, 0.82 mL) and cyclohexanone (1.25 g, 12.74 mmol, 1.33 mL) were added under nitrogen and the reaction was heated to 80 °C for 24 hours. After cooling, the reaction mixture was diluted with diethyl ether (*ca.* 10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (5 to 10% diethyl ether:petrol) to yield ketone **111** (0.94 g, 58%) as a white solid: mp 57-58 °C (Lit. 58-59 °C).[13] ν_{max} (Nujol™)/cm^{-1} 2920, 2855, 1709, 1566w, 1462, 1377, 1281, 1196, 1121, 1070, 1027, 977, 940, 769, 746, 722, 674; δ_H (300 MHz, $CDCl_3$) 1.71-2.10 (4H, m, C*H*$_2$), 2.15-2.35 (2H, m, ArCHC*H*$_2$), 2.51-2.89 (2H, m, C*H*$_2$CO), 4.11 (1H, app. dd, *J* 12.4 and 5.3, Ar-C*H*), 7.12 (1H, ddd, *J* 7.9, 7.2 and 1.9, Ar-*H*), 7.21 (1H, dd, *J* 7.9 and 1.9, Ar-*H*), 7.31 (1H, td, *J* 7.9 and 1.1, Ar-*H*), 7.56 (1H, td, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 25.1, 27.1, 33.6, 41.8, 56.0, 124.6, 126.8, 127.8, 128.9, 132.1, 137.8, 208.3; *m/z* LRMS (CI^+, NH_3) 270 $[M+NH_4]^+$, 253 $[M+H:^{79}Br]^+$, 173 $[M-^{79}Br]^+$, 145 $[M-^{79}Br\text{-}CO]^+$, 115 $[M-^{79}Br\text{-}CO\text{-}C_2H_4]^+$; HRMS ($ES^+$) calc. for $C_{12}H_{14}BrO$: 253.0223 $[M+H]^+$; found: 253.0225 $[M+H]^+$.

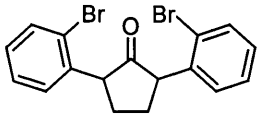
Preparation of **2-(2-chlorophenyl)-cyclohexanone, 123**



General procedure B was followed employing 1-bromo-2-chlorobenzene (1.00 g, 5.22 mmol, 0.61 mL) and cyclohexanone (1.03 g, 10.45 mmol, 1.08 mL), heating at 100 °C for 20 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield *ketone* **123** (640 mg, 59%) as a creamy white coloured solid: mp 60-62 °C; ν_{max} (KBr)/cm^{-1} 2938, 2869, 1709, 1560, 1477, 1443, 1430, 1296, 1290, 1197, 1123, 1070, 1051, 1035, 769, 749; δ_H (300 MHz, $CDCl_3$) 1.65-1.90 (2H, m, C*H*$_2$), 1.90-2.04 (2H, m, C*H*$_2$), 2.08-2.29 (2H, m, ArCHC*H*$_2$), 2.40-2.53 (2H, m, C*H*$_2$CO), 4.03 (1H, app. dd, *J* 12.4 and 5.3, Ar-C*H*), 7.08-7.23 (3H, m, Ar-*H*), 7.30 (1H, d, *J* 7.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 26.1, 28.1, 34.3, 42.8, 54.4, 127.2, 128.5, 129.7, 129.8, 134.6, 137.1, 209.3; *m/z* LRMS (EI$^+$) 211 [M:^{37}Cl]$^+$ (24%), 209 [M:^{35}Cl]$^+$ (80%), 174 [M+H-^{35}Cl]$^+$ (33%), 173 [M-^{35}Cl]$^+$ (100%), 164 [M]$^+$ (44%), 151 [M-C_3H_6O]$^+$ (26%), 145 [M-CO:^{35}Cl]$^+$ (47%), 138 (51%), 129 (100%): (CI$^+$, NH_3) 228 [M+NH_4:^{37}Cl]$^+$, 226 [M+NH_3:^{35}Cl]$^+$; HRMS (ES$^+$) calc. for $C_{12}H_{17}ClNO$: 226.0993 [M+NH_4]$^+$; found: 226.0995 [M+NH_4]$^+$. $C_{12}H_{13}ClO$ requires C 69.07, H 6.28%, found C 68.70, H 6.02%.

Preparation of **2-(2-bromophenyl)-cyclopentanone, 119; 2,5-*bis*-(2-bromophenyl)-cyclopentanone, 120**

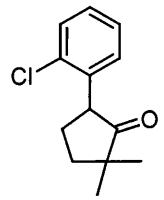




General procedure B was followed employing 1-bromo-2-iodobenzene (1.80 g, 6.37 mmol, 0.82 mL) and cyclopentanone (1.07 g, 1.27 mmol, 1.13 mL), heating at 120 °C for 20 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield *ketone* **119** (0.54 g, 35%) as a pale amber oil and *ketone* **120** (0.144 g, 6%) as a pale yellow oil. *Ketone* **119**: ν_{max} (NaCl)/cm^{-1} 3057, 2964, 2879, 1738, 1591, 1566, 1475, 1438, 1404, 754, 733; δ_H (300 MHz, $CDCl_3$) 1.96-2.01 (2H, m, C*H*$_2$), 2.14-2.20 (1H, m, ArCHC*H*$_2$), 2.35-2.42 (1H, m, ArCHC*H*$_2$), 2.47-2.57 (2H, m,

CH_2CO), 3.76 (1H, app. dd, *J* 10.6 and 8.4, Ar-C*H*), 7.06 (1H, dd, *J* 7.7 and 1.8, Ar-*H*), 7.11 (1H, dd, *J* 7.7 and 1.8, Ar-*H*), 7.26 (1H, td, *J* 7.8 and 1.1, Ar-*H*), 7.56 (1H, dd, *J* 8.1 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 21.4, 32.2, 39.0, 56.6, 125.3, 128.0, 128.7, 129.9, 133.2, 138.9, 217.5; *m/z* LRMS (EI^+) 241 $[M+H:^{81}Br]^+$ (16%), 240 $[M+H:^{81}Br]^+$ (90%), 239 $[M+H:^{79}Br]^+$ (17%), 238 $[M:^{79}Br]^+$ (100%), 159 $[M-^{79}Br]^+$ (92%), 131 $[M-^{79}Br\text{-}CO]^+$ (100%), 117 $[M-^{79}Br\text{-}C_2H_2O]^+$ (60%), 103 $[M-^{79}Br\text{-}C_3H_4O]^+$ (94%), 89 $[M-^{79}Br\text{-}C_4H_6O]^+$ (36%), 77 $[C_6H_5]$ (82%): (CI^+, NH_3) 257 $[M+NH_4:^{79}Br]^+$, 256 $[M+NH_3:^{79}Br]^+$, 178 $[M+NH_4\text{-}^{79}Br]^+$: HRMS ($ES^+$) calc. for $C_{11}H_{15}BrNO$: 256.0332 $[M+NH_4:\ ^{79}Br]^+$; found: 256.0328 $[M+NH_4:\ ^{79}Br]^+$. *Ketone* **120**: ν_{max} (Nujol™)/cm^{-1} 3059, 2963, 1739, 1590, 1566, 1450, 1439, 1346, 1265, 1147, 1122, 1023, 828, 756; δ_H (300 MHz, $CDCl_3$) impure: 1.99-2.05 (2H, m, CH_2CO), 2.55-2.61 (2H, m, CH_2CO), 3.92 (2H, app. dd, *J* 11.8 and 8.2, Ar-C*H*), 7.00-7.06 (4H, m, Ar-*H*), 7.19 (2H, app. td, *J* 7.7 and 1.2, Ar-*H*), 7.47 (2H, dd, *J* 7.7 and 1.2, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 30.3, 57.4, 125.2, 128.1, 128.9, 130.0, 133.3, 138.9, 214.6; *m/z* LRMS (EI^+) 396 $[M:^{81}Br]^+$ (48%), 394 $[M:^{79/81}Br]^+$ (100%), 392 $[M:^{79}Br]^+$ (50%): (CI^+, NH_3) 414 $[M+NH_4:^{81}Br]$, 412 $[M+NH_4:^{79/81}Br]^+$, 410 $[M+NH_4:^{79}Br]^+$, 334 $[M+NH_3\text{-}^{79}Br]^+$, 332 $[M+NH_3\text{-}^{81}Br]^+$, 254 $[M+NH_3\text{-}^{79}Br_2]^+$, 178 $[M+NH_3\text{-}^{79}Br_2\text{-}C_6H_4]^+$: HRMS ($ES^+$) calc. for $C_{11}H_{15}BrNO$: 409.9750 $[M+NH_4]^+$; found: 409.9746 $[M+NH_4]^+$.

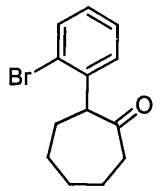
Preparation of **5-(2-chlorophenyl)-2,2-dimethylcyclopentanone, 125**



General procedure B was followed employing 1-bromo-2-chlorobenzene (159 mg, 0.83 mmol, 0.10 mL), 2,2-dimethylcyclopentanone (112 mg, 0.10 mmol, 0.13 mL) and 2-(dicyclohexylphosphino)-2'-methylbiphenyl **5a** (18 mg, 0.05 mmol) as the ligand, heating at 110 °C for 17 hours. The product was purified *via* flash column chromatography (5 to 10% diethyl ether:petrol) to yield *ketone* **125** (90 mg, 50%) as a creamy/white solid: mp 63-64 °C; ν_{max} (KBr)/cm^{-1} 2961, 2867, 1736, 1478, 1460, 1437, 1381, 1360, 1329, 1258, 1190, 1128, 1089, 1062, 1031, 767, 753; δ_H (300 MHz, $CDCl_3$) 1.15 (3H, s, C(CH_3)$_2$), 1.20 (3H, s, C(CH_3)$_2$), 1.81-2.07 (3H, m, CH_2 and ArCHCH_2), 2.42-2.53 (1H, m, ArCHCH_2), 3.85-3.97 (1H, m, Ar-C*H*), 7.03 (1H, dd, *J* 7.5 and 2.1,

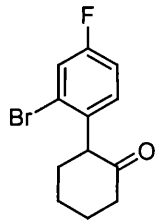
Ar-*H*), 7.18 (1H, td, *J* 7.5 and 1.9, Ar-*H*), 7.23 (1H, td, *J* 7.5 and 1.9, Ar-*H*), 7.38 (1H, dd, *J* 7.5 and 2.1, Ar-*H*); δ_C (75 MHz, $CDCl_3$); 24.2, 25.5, 28.1, 37.0, 45.8, 53.1, 127.5, 128.6, 129.6, 130.0, 135.0, 137.9, 221.5; *m/z* LRMS (CI^+, NH_3) 242 $[M:^{37}Cl]^+$, 240 $[M:^{35}Cl]^+$, 206 $[M-^{35}Cl]^+$, 204 $[M-^{37}Cl]^+$: HRMS (ES^+) calc. for $C_{13}H_{19}ClNO$: 240.1150 $[M+NH_4]^+$, found: 240.1153 $[M+NH_4]^+$. $C_{13}H_{15}ClO$ requires C 70.11, H 6.79%, found C 69.80, H 6.78%.

Preparation of **2-(2-bromophenyl)-cycloheptanone, 127**



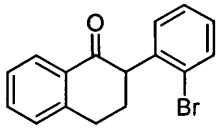
General procedure B was followed employing 1-bromo-2-iodobenzene (1.80 g, 6.37 mmol, 0.82 mL) and cycloheptanone (1.43 g, 1.27 mmol, 1.50 mL) using NaHMDS (14.00 mmol, 14.00 mL) as the base, heating at 100 °C for 24 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield *ketone* **127** (1.57 g, 62%) as an amber oil. ν_{max} (NaCl)/cm^{-1} 3062, 2928, 2800, 1705, 1470, 1445, 1439, 1217, 1156, 1134, 1022, 934, 746; δ_H (300 MHz, $CDCl_3$) 1.32-1.75 (2H, m, C*H*$_2$), 1.72-2.18 (6H, m, C*H*$_2$ and ArCHC*H*$_2$), 2.50-2.94 (2H, m, C*H*$_2$CO), 4.39 (1H, app. dd, *J* 10.9 and 2.6, Ar-C*H*), 7.11 (1H, td, *J* 7.9 and 2.3, Ar-*H*), 7.24-7.34 (2H, m, Ar-*H*), 7.55 (1H, dd *J* 7.9 and 1.1, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 24.2, 29.5, 30.2, 32.4, 44.8, 57.0, 124.9, 127.9, 128.6, 130.0, 132.9, 141.3, 213.2; *m/z* LRMS (CI^+, NH_3) 286 $[M+NH_3:{}^{79}Br]^+$, 267 $[M]^+$, 206 $[M+NH_4-{}^{79}Br]^+$, 187 $[M-{}^{79}Br]^+$: HRMS (ES^+) calc. for $C_{13}H_{19}BrNO$: 284.0645 $[M+NH_4:{}^{79}Br]^+$; found: 284.0651 $[M+NH_4:{}^{79}Br]^+$.

Preparation of **2-(2-bromo-4-fluorophenyl)-cyclohexanone, 129**



General procedure B was followed employing 2-bromo-4-fluoroiodobenzene (500 mg, 1.66 mmol, 0.22 mL) and cyclohexanone (330 mg, 3.32 mmol, 0.34 mL), heating at 110 °C for 21 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield *ketone* **129** (140 mg, 30%) as white prisms: mp 86-88 °C. ν_{max} (KBr)/cm^{-1} 3392, 2940, 2897, 2871, 2853, 1702, 1603, 1578, 1467, 1459, 1441, 1410, 1265, 1219, 1162, 1126, 1084, 1031, 1003, 875, 806; δ_H (300 MHz, $CDCl_3$) 1.72-2.09 (4H, m, C*H*$_2$), 2.16-2.33 (2H, m, ArCHC*H*$_2$), 2.52-2.59 (2H, m, C*H*$_2$CO), 4.08 (1H, app. dd, *J* 12.2 and 5.1, Ar-C*H*), 7.04 (1H, td, *J* 8.3 and 2.6, Ar-*H*), 7.19 (1H, dd, *J* 8.7 and 6.0, Ar-*H*), 7.32 (1H, dd, *J* 8.7 and 2.6, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 20.1, 25.2, 34.9, 42.8, 56.3, 115.0 (d, J_{CF} 20.3), 120.2 (d, J_{CF} 24.0), 125.3 (d, J_{CF} 9.0), 130.7 (d, J_{CF} 8.3), 134.7 (d, J_{CF} 3.8), 161.6 (d, J_{CF} 248.3), 208.2; *m/z* LRMS (ES$^+$) 273 [M+H:^{81}Br] (25%), 255 (20%), 203 (50%), 189 (100%), 174 (20%), 148 (10%); HRMS (ES$^+$) calc. for $C_{12}H_{16}BrFNO$: 288.0391 [M+NH$_4$:^{79}Br]$^+$; found: 288.0394 [M+NH$_4$:^{79}Br]$^+$.

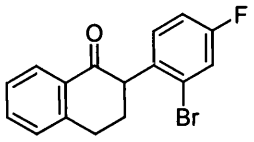
Preparation of **2-(2-bromophenyl)-3,4-dihydro-*2H*-naphthalen-1-one, 131**



General procedure B was followed employing 1-bromo-2-iodobenzene (3.60 g, 12.74 mmol, 1.63 mL) and α-tetralone (2.24 g, 15.29 mmol, 2.04 mL) using sodium *tert*-butoxide (1.59 g, 16.56 mmol) as the base, heating at 110 °C for 24 hours. The product was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *ketone* **131** (2.00 g, 52%) as a viscous yellow oil. ν_{max} (film)/cm^{-1} 3062, 2933, 2871, 1683, 1600, 1566, 1474, 1455, 1435, 1355, 1299, 1223, 1156, 1107, 1025, 898, 745, 685; δ_H (300 MHz, $CDCl_3$) 2.24-2.46 (2H, m, ArCHC*H*$_2$), 2.99 (1H, dt, *J* 16.6 and 4.1, Ar-C*H*$_2$), 3.15 (1H, dd, *J* 10.9 and 4.9, Ar-C*H*$_2$), 4.25 (1H, app. dd, *J* 11.9 and 4.9, Ar-C*H*), 7.03-7.12 (2H, m, Ar-*H*), 7.18-7.32 (3H, m, Ar-*H*), 7.45 (1H, td, *J* 7.9 and 1.1, Ar-*H*), 7.54 (1H, dd, *J* 7.9 and 1.1, Ar-*H*), 8.04 (1H, dd, *J* 7.9 and 1.1, Ar-*H*); δ_C (75 MHz,

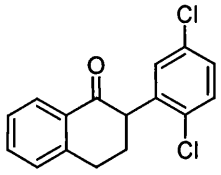
$CDCl_3$) 29.8, 30.9, 54.8, 66.3, 125.7. 127.6, 128.0, 128.2, 128.9, 129.2, 130.0, 133.3, 133.4, 133.9, 140.1, 144.3, 197.3; *m/z* LRMS (CI^+, NH_3) 320 $[M+NH_4:^{81}Br]^+$, 301 $[M+H:^{79}Br]^+$, 240 $[M+NH_3-^{81}Br]^+$, 221 $[M-^{79}Br]^+$; HRMS (ES^+) calc. for $C_{16}H_{17}BrNO$: 318.0488 $[M+NH_4:^{79}Br]^+$; found: 318.0488 $[M+NH_4:^{79}Br]^+$.

Preparation of **2-(2-bromo-4-fluorophenyl)-3,4-dihydro-*2H*-naphthalen-1-one, 133**



General procedure B was followed employing 2-bromo-5-fluoroiodobenzene (130 mg, 0.42 mmol, 0.05 mL) and α-tetralone (70 mg, 0.50 mmol, 0.07 mL), heating at 110 °C for 16 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield *ketone* **133** (90 mg, 57%) as a white crystalline solid: mp 78-79 °C. ν_{max} (KBr)/cm^{-1} 3065, 2962, 1679, 1599, 1579, 1469, 1455, 1428, 1410, 1294, 1265, 1218, 1166, 1144, 1025, 1011, 869, 824, 809, 758, 749; δ_H (300 MHz, $CDCl_3$) 2.36-2.52 (2H, m, ArCHCH_2), 3.10 (1H, dt, *J* 16.8 and 4.1, Ar-CH_2), 3.26 (1H, ddd, J 16.8, 10.7 and 5.7, Ar-CH_2), 4.31 (1H, app. dd, *J* 10.7 and 5.7, Ar-C*H*), 6.87-6.97 (2H, m, Ar-*H*), 7.33 (1H, d, *J* 7.9, Ar-*H*), 7.38 (1H, t, *J* 7.9, Ar-*H*), 7.55 (1H, t, *J* 7.9, Ar-H), 7.59 (1H, dd, *J* 7.9 and 5.5, Ar-*H*), 8.13 (1H, d, *J* 7.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 29.8, 30.7, 54.8, 116.2 (d, J_{CF} 22.6), 117.1 (d, J_{CF} 23.4), 119.8 (d, J_{CF} 3.0), 127.3, 128.3, 129.2, 133.6 (d, J_{CF} 78.5), 134.3 (d, J_{CF} 8.3), 142.0 (d, J_{CF} 7.6), 144.1, 160.7, 164.0, 196.6; *m/z* LRMS (CI^+, NH_3) 338 $[M+NH_4:^{81}Br]^+$, 336 $[M+NH_4:^{79}Br]^+$, 321 $[M+H:^{81}Br]^+$, 319 $[M+H:^{79}Br]$: HRMS (ES^+) calc. for $C_{16}H_{16}BrFNO$: 336.0394 $[M+NH_4:^{79}Br]^+$; found: 336.0390 $[M+NH_4:^{79}Br]^+$.

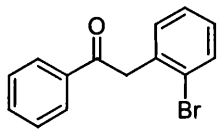
Preparation of **2-(2,5-dichlorophenyl)-3,4-dihydro-*2H*-naphthalen-1-one, 135**



General procedure B was followed employing 1-bromo-2,5-dichlorobenzene (190 mg, 0.83 mmol), α-tetralone (150 mg, 1.00 mmol, 0.13 mL) and sodium *tert*-butoxide (120 mg, 1.24 mmol) as the base, heating at 110 °C for 24 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:heptane) to yield *ketone* **135**

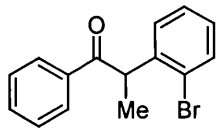
(150 mg, 67%) as a white crystalline solid: mp 98-100 °C. ν_{max} (KBr)/cm^{-1} 3060, 3018, 2943, 1683, 1597, 1467, 1453, 1437, 1390, 1354, 1296, 1263, 1221, 1154, 1096, 1035, 1012, 966, 909, 878, 817, 753; δ_H (300 MHz, $CDCl_3$) 2.22-2.49 (2H, m, ArCHC*H*$_2$), 3.08 (1H, dt, *J* 16.7 and 3.8, Ar-C*H*$_2$), 3.23 (1H, ddd, *J* 16.7, 12.4 and 4.6, Ar-C*H*$_2$), 4.24 (1H, dd, *J* 12.4 and 4.6, Ar-C*H*), 7.19 (1H, dd, *J* 3.5 and 0.9, Ar-*H*), 7.22 (1H, d, *J* 2.6, Ar-*H*), 7.31 (1H, d, *J* 7.5, Ar-*H*), 7.35 (1H, dd, *J* 8.1 and 0.9, Ar-*H*), 7.37 (1H, d, *J* 7.5, Ar-*H*), 7.53 (1H, td, *J* 7.5 and 1.5, Ar-*H*), 8.10 (1H, dd, *J* 8.1 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 29.9, 30.4, 52.5, 127.3, 128.3, 128.8, 129.2, 130.0, 131.0, 133.0, 133.2, 134.1, 140.0, 144.1, 196.6; *m/z* LRMS (CI^+, NH_3) 312 $[M+NH_3{:}^{37}Cl]^+$, 310 $[M+NH_3{:}^{35/37}Cl]^+$, 308 $[M+NH_3{:}^{35}Cl]^+$, 293 $[M{:}^{35/37}Cl]^+$, 291 $[M{:}^{35}Cl]^+$, 276 $[M\text{-}OH{:}^{35/37}Cl]^+$, 274 $[M\text{-}OH{:}^{35}Cl]^+$; HRMS ($ES^+$) calc. for $C_{16}H_{16}Cl_2NO$: 308.0603 $[M+NH_4{:}^{35}Cl]^+$; found: 308.0600 $[M+NH_4{:}^{35}Cl]^+$.

Preparation of **2-(2-bromophenyl)-1-phenylethanone, 137**



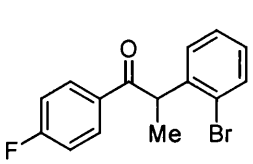
General procedure B was followed employing 1-bromo-2-iodobenzene (2.00 g, 7.07 mmol, 0.91 mL) and acetophenone (1.02 g, 8.48 mmol, 0.99 mL) using $HP^tBu_3BF_4$ (90 mg, 0.32 mmol) as the ligand and sodium *tert*-butoxide (1.60 g, 16.56 mmol) as the base, heating at 60 °C for 9 hours. The product was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *ketone* **137** (1.19 g, 51%) as a white crystalline solid: mp 66-67 °C. ν_{max} (Nujol™)/cm^{-1} 3057, 1691, 1585, 1581, 1567, 1470, 1447, 1427, 1407, 1331, 1277, 1219, 1202, 1174, 1156, 1025, 990, 756, 690, 666, 650, 575; δ_H (300 MHz, $CDCl_3$) 4.46 (2H, s, Ar-C*H*$_2$CO), 7.15 (1H, ddd, *J* 7.9, 6.8 and 2.3, Ar-*H*), 7.22-7.32 (2H, m, Ar-*H*), 7.47 (2H, tt, *J* 8.1 and 1.5, Ar-*H*), 7.55-7.62 (2H, m, Ar-*H*), 8.05 (2H, d, *J* 7.2, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 45.8, 125.1, 127.5, 128.3, 128.7, 131.7, 132.8, 133.3, 133.8, 134.9, 136.6, 196.3; *m/z* LRMS (CI^+, NH_3) 294 $[M+NH_4{:}^{81}Br]^+$, 292 $[M+NH_4{:}^{79}Br]^+$, 277 $[M+NH_3{:}^{81}Br]^+$, 275 $[M+NH_3{:}^{79}Br]^+$; HRMS (ES^+) calc. for $C_{14}H_{15}BrNO$: 292.0332 $[M+NH_4{:}^{79}Br]^+$; found: 292.0331 $[M+NH_4{:}^{79}Br]^+$; $C_{14}H_{11}OBr$ requires C 61.11, H 4.03%, found C 61.10, H 4.01%.

Preparation of **2-(2-bromophenyl)-1-phenylpropan-1-one, 139**



General procedure B was followed employing 1-bromo-2-iodobenzene (3.60 g, 12.74 mmol, 1.63 mL) and propiophenone (2.05 g, 15.29 mmol, 2.03 mL) using $HP^tBu_3BF_4$ (90 mg, 0.32 mmol) as the ligand and sodium *tert*-butoxide (1.60 g, 16.56 mmol) as the base, heating at 60 °C for 9 hours. The product was purified *via* flash column chromatography (2.5% diethyl ether:petrol) to yield *ketone* **139** (2.62 g, 71%) as white prisms: mp 51-53 °C (MeOH) (49-50 °C). ν_{max} (Nujol™)/cm^{-1} 2926, 2855, 1676, 1597, 1581, 1455, 1374, 1327, 1250, 1226, 1181, 1024, 1001, 951, 756, 702, 685, 661; δ_H (300 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, CHC*H*$_3$), 5.11 (1H, q, *J* 6.8, COC*H*CH$_3$), 7.03-7.24 (3H, m, Ar-*H*), 7.35-7.42 (2H, m, Ar-*H*), 7.45-7.52 (1H, m, Ar-*H*), 7.60 (1H, dd, *J* 7.9 and 1.1, Ar-*H*), 7.93 (1H, dd, *J* 7.2 and 1.5, Ar-*H*), 7.94 (1H, dd, *J* 8.3 and 2.3, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 18.3, 47.5, 124.4, 128.6, 128.93, 128.99, 129.0, 129.1, 133.4, 133.7, 136.4, 141.4, 200.5; *m/z* LRMS (CI$^+$, NH_3) 308 $[M+NH_4]^+$, 289 $[M+H]^+$, 228, 209, 139, 105; HRMS (ES$^+$) calc. for $C_{15}H_{17}BrNO$: 289.0223 $[M+NH_4{:}^{79}Br]^+$; found: 289.0227 $[M+NH_4{:}^{79}Br]^+$; $C_{15}H_{13}BrO$ requires C 62.30, H 4.53%, found C 62.40, H 4.65%. Data are in agreement with literature values.[14]

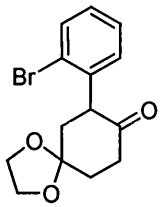
Preparation of **2-(2-bromophenyl)-1-(4-fluorophenyl)propan-1-one, 141**



General procedure B was followed employing 1-bromo-2-iodobenzene (1.80 g, 6.37 mmol, 0.82 mL) and 4'-fluoropropiophenone (1.16 g, 7.64 mmol, 1.06 mL) using $HP^tBu_3BF_4$ (46 mg, 0.16 mmol) as the ligand and sodium *tert*-butoxide (0.80 g, 8.28 mmol) as the base, heating at 60 °C for 6 hours. The product was purified *via* flash column chromatography (0 to 5% diethyl ether:cyclohexane) to yield *ketone* **141** (1.18 g, 60%) as a pale amber oil. ν_{max} (film)/cm^{-1} 3069, 2980, 2933, 1684, 1596, 1506, 1470, 1439, 1409, 133, 1224, 1156, 1021, 952, 849, 796, 751, 689; δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, CHC*H*$_3$), 5.06 (1H, q, *J* 6.8, COC*H*CH$_3$), 7.01-7.42 (4H, m, Ar-*H*), 7.19 (1H, app. dd, *J* 7.5 and 7.0, Ar-*H*), 7.60 (1H, d, *J* 8.0, Ar-*H*), 7.96 (2H, dd, *J* 8.5 and 5.5, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 17.9, 47.1, 115.7 (d, J_{CF} 21.6), 123.9, 128.2, 128.6,

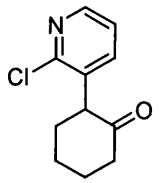
128.6, 131.4, (d, J_{CF} 9.6), 132.4, 133.3, 140.8, 165.6 (d, J_{CF} 255.7), 196.5; *m/z* LRMS (CI^+, NH_3) 324 $[M+NH_4:^{79}Br]^+$, 307 $[M:^{79}Br]^+$, 246, 123; HRMS (ES^+) calc. for $C_{15}H_{13}BrFO$: 307.0128 $[M+H:^{79}Br]^+$; found: 307.0130 $[M+H:^{79}Br]^+$.

Preparation of **7-(2-bromophenyl)-1,4-dioxa-spiro[4,5]decan-8-one, 143**



General procedure B was followed using 1-bromo-2-iodobenzene (3.60 g, 12.74 mmol, 1.63 mL) and 1,4-cyclohexanedione monoethylene ketal (3.98 g, 25.48 mol), heating at 100 °C for 24 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield *ketone* **143** (2.30 g, 58%) as white prisms: mp 98-100 °C (DCM/hexane). ν_{max} (Nujol™)/cm^{-1} 2923, 2854, 1719, 1569, 1465, 1377, 1308, 1121, 1064, 1026, 953, 766, 722; δ_H (300 MHz, $CDCl_3$) 2.10-2.29 (3H, m, ArCHCH_2 and CCH_2), 2.35 (1H, t, *J* 13.6, ArCHCH_2), 2.53 (1H, app. dt, *J* 14.6 and 3.3, CH_2CO), 2.80-2.94 (1H, m, CH_2CO), 3.99-4.15 (4H, m, O(CH_2)$_2$O), 4.47 (1H, app. dd, *J* 13.6 and 5.5, Ar-C*H*), 7.20-7.18 (2H, m, Ar-*H*), 7.31 (1H, ddd, *J* 8.0, 7.0 and 0.8, Ar-*H*), 7.57 (1H, dd, *J* 8.0 and 0.8. Ar-*H*); δ_C (75 MHz, $CDCl_3$) 34.7, 38.5 40.5, 52.6, 64.8, 64.9, 107.3, 125.3, 127.5, 128.7, 129.5, 132.9, 137.3, 207.4; *m/z* LRMS (CI^+, NH_3) 330 $[M+NH_4:^{81}Br]^+$, 311 $[M+H:^{79}Br]^+$, 250 $[M-C_2H_4O_2:^{79}Br]^+$, 217, 141 $[M-^{79}Br-C_3H_6O_3]$, 86; HRMS (ES^+) calc. for $C_{14}H_{19}BrNO_3$: 328.0543 $[M+NH_4:^{79}Br]^+$; found: 328.0548 $[M+NH_4:^{79}Br]^+$; $C_{14}H_{15}O_3Br$ requires C 54.04, H 4.86%, found C 54.00, H 4.84%.

Preparation of **2-(2-chloropyridin-3-yl)-cyclohexanone, 145**

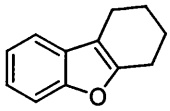


General procedure B was followed employing 3-bromo-2-chloropyridine (250 mg, 1.27 mmol) and cyclohexanone (250 mg, 2.55 mmol, 0.27 mL), heating at 100 °C for 24 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield *ketone* **145** (90 mg, 35%) as white prisms: mp 109-110 °C

(DCM/hexane). ν_{max} (Nujol™)/cm^{-1} 3505, 2923, 2854, 1705, 1581, 1567, 1450, 1409, 1377, 1289, 1186, 1096, 1055, 806, 737; δ_H (300 MHz, $CDCl_3$) 1.73-1.99 (3H, m, C*H*$_2$), 2.02-2.13 (1H, m, C*H*$_2$), 2.18-2.37 (2H, m, ArCHC*H*$_2$), 2.53-2.62 (2H, m, C*H*$_2$CO), 4.11 (1H, app. dd, *J* 12.2 and 5.5, Ar-C*H*), 7.26 (1H, dd, *J* 7.9 and 4.9, Ar-*H*), 7.59 (1H, dd, *J* 7.9 and 1.9, Ar-*H*), 8.31 (1H, dd, *J* 4.9 and 1.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 25.9, 29.1, 37.5, 42.7, 54.0, 122.9, 133.8, 138.8, 148.3, 151.8, 208.5; *m/z* LRMS (EI$^+$) 209 [M:^{35}Cl]$^+$ (15%), 174 [M-^{35}Cl]$^+$ (100%), 146 [M-^{35}Cl-CO]$^+$ (70%), 139 [M-C_4H_6O]$^+$ (80%), 130 [M-^{35}Cl-C_2H_4O]$^+$ (90%), 117 [M-^{35}Cl-C_3H_5O] (80%), 104 [M-^{35}Cl-C_4H_6O] (80%); HRMS (ES$^+$) calc. for $C_{11}H_{12}NClO$: 209.0602 [M:^{35}Cl]$^+$; found: 209.0602 [M:^{35}Cl]$^+$.

Preparation of Benzofurans by Palladium Catalysis

Preparation of **1,2,3,4-tetrahydro-dibenzofuran, 89**



General Procedure C:

Cesium carbonate (180 mg, 0.56 mmol) was added to a flask charged with $Pd_2(dba)_3$ (9 mg, 0.01 mmol) and DPEphos (13 mg, 0.02 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (1 mL) prior to the addition of *ketone* **111** (100 mg, 0.40 mmol) and the reaction heated to 100 °C for 20 hours. After cooling the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of celite and the filtrate reduced *in vacuo*. The residue was purified *via* flash column chromatography (petrol) to yield benzofuran **89** (64 mg, 95%) as a colourless oil.

Tandem Palladium Catalysed One-Pot Reactions

Cesium carbonate (1.73 g, 5.30 mmol) was added to a flask charged with $Pd_2(dba)_3$ (81 mg, 0.09 mmol), Xantphos (61 mg, 0.11 mmol) and DPEphos (57 mg, 0.11 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (2.00 mL) and 1-bromo-2-iodobenzene (0.50 g, 1.77 mmol, 0.23 mL) and cyclohexanone (0.26 g, 2.65 mmol, 0.28 mL) were added under nitrogen and the reaction was heated to 100 °C for 48 hours. After cooling, the reaction mixture was diluted with diethyl ether (*ca.* 10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash

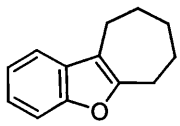
column chromatography (petrol) to yield benzofuran **89** (0.18 g, 41%) as a colourless oil.

General Procedure D:

Cesium carbonate (691 mg, 2.21 mmol) was added to a flask charged with $Pd_2(dba)_3$ (32 mg, 0.04 mmol) and S-phos (17 mg, 0.04 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (1.00 mL) and 1-bromo-2-iodobenzene (200 mg, 0.71 mmol, 0.09 mL) and cyclohexanone (80 mg, 0.85 mmol, 0.09 mL) were added under nitrogen and the reaction was heated to 100 °C for 48 hours. After cooling, the reaction mixture was diluted with diethyl ether (*ca.* 10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (petrol) to yield benzofuran **89** (111 mg, 91%) as a colourless oil.

ν_{max} (NaCl)/cm^{-1} 3060, 2927, 2849, 1741, 1640, 1614, 1453, 1363, 1298, 1275, 1257, 1223, 1190, 1122, 1009, 876, 820, 743; δ_H (300 MHz, $CDCl_3$) 1.72-1.82 (2H, m, C*H*$_2$), 1.82-1.92 (2H, m, C*H*$_2$), 2.55 (2H, app. tt, *J* 6.0 and 1.9, C*H*$_2$C=CO), 2.67 (2H, app. tt, *J* 6.0 and 1.9, C*H*$_2$CO=C), 7.06-7.16 (2H, m, Ar-*H*), 7.28-7.35 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 20.9, 23.1, 23.4, 23.5, 111.2, 113.2, 118.7, 122.5, 123.3, 129.3, 154.4, 154.7; *m/z* LRMS (EI$^+$) 172 [M]$^+$ (44%), 144 [M-CO]$^+$, 115 [M-C_3H_5O] (44%), 69 [M-$C_6H_{13}O$]$^+$ (39%); HRMS (EI) calc. for $C_{12}H_{12}O$: 172.0883 [M]$^+$; found: 172.0882 [M]$^+$. Data are in agreement with literature values.[15]

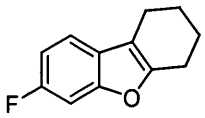
Preparation of **6,7,8,9-tetrahydro-5*H*-10-oxa-benzo[α]azulene, 128**



General procedure C was followed employing *ketone* **127** (100 mg, 0.37 mmol), using NaHMDS (0.80 mmol, 0.80 mL) as the base and heating at 110 °C for 20 hours. The product was purified *via* flash column chromatography (petrol) to yield benzofuran **128** (63 mg, 95%) as a colourless oil. ν_{max} (Nujol™)/cm^{-1} 3036, 2923, 2849, 1626, 1610, 1587, 1475, 1455, 1368, 1308, 1278, 1240, 1228, 1210, 1147, 1096, 1070, 1037, 1009, 815, 743; δ_H (300 MHz, $CDCl_3$) 1.65-1.87 (6H, m, C*H*$_2$), 2.62 (2H, app. t, *J* 5.7, C*H*$_2$C=CO), 2.85 (2H, app. t, *J* 5.7, C*H*$_2$CO=C), 7.07-7.14 (2H, m, Ar-*H*), 7.25-7.35 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 23.6, 26.8, 28.7, 29.5, 31.0, 110.9, 116.2, 118.6, 122.3, 123.2, 130.9, 153.7, 156.8; *m/z* LRMS (EI$^+$) 186 [M]$^+$ (54%), 158 [M-CO]$^+$ (42%), 157 [M-CHO]$^+$ (75%), 144 (54%), 128 (60%), 115 (100%); (CI$^+$, NH_3) 187

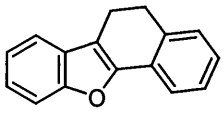
$[M+H]^+$; HRMS (ES^+) calc. for $C_{13}H_{15}O$: 187.1117 $[M+H]^+$; found: 187.1119 $[M+H]^+$. Data are in agreement with literature values.[16]

Preparation of **8-fluoro-1,2,3,4-tetrahydro-dibenzofuran, 130**



General procedure C was followed employing *ketone* **129** (500 mg, 1.84 mmol), heating at 100 °C for 22 hours. The product was purified *via* flash column chromatography (petrol) to yield *benzofuran* **130** (221 mg, 63%) as a colourless oil. ν_{max} (Nujol™)/cm^{-1} 3081, 2934, 2847, 1645, 1621, 1599, 1489, 1443, 1428, 1361, 1330, 1296, 1269, 1256, 1194, 1116, 1100, 942, 872, 838, 803; δ_H (300 MHz, $CDCl_3$) 1.80-1.99 (4H, m, C*H*$_2$), 2.57-2.64 (2H, m, C*H*$_2$C=CO), 2.70-2.77 (2H, m, C*H*$_2$CO=C), 6.92-7.00 (1H, m, Ar-*H*), 7.13 (1H, dd, *J* 8.7 and 1.9, Ar-*H*), 7.30 (1H, dd, *J* 8.7 and 5.4, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 20.8, 23.0, 23.2, 23.8, 99.1 (d, J_{CF} 26.7), 110.4 (d, J_{CF} 23.6), 113.0, 118.7 (d, J_{CF} 9.9), 125.5, 154.6, 155.0 (d, J_{CF} 4.3), 160.6 (d, J_{CF} 239.4); *m/z* LRMS (EI^+) 190 $[M]^+$ (36%), 162 $[M-CO]^+$ (100%), 133 $[M-C_3H_5O]^+$ (60%); (CI^+, NH_3) 191 $[M+H]^+$, 190 $[M-H]^+$, 162 $[M-CO]^+$; HRMS (ES^+) calc. for $C_{12}H_{12}FO$: 191.0867 $[M+H]^+$; found: 191.0866 $[M+H]^+$.

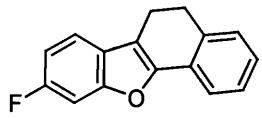
Preparation of **5,6-dihydrobenzo[β]naphtho[2,1-δ]furan, 132**



General procedure C was followed employing *ketone* **131** (100 mg, 0.26 mmol), using NaHMDS (0.38 mmol, 0.38 mL) as the base and heating at 100 °C for 19 hours. The product was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *benzofuran* **132** (42 mg, 81%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3053, 2933, 2846, 1485, 1456, 1443, 1425, 1357, 1302, 1280, 1263, 1184, 1138, 1114, 1087, 926, 868, 827, 741; δ_H (300 MHz, $CDCl_3$) 2.96 (2H, t, *J* 7.9, C=CC*H*$_2$), 3.11 (2H, t, *J* 7.9, Ar-C*H*$_2$), 7.18-7.33 (5H, m, Ar-*H*), 7.49-7.55 (2H, m, Ar-*H*), 7.66 (1H, d, *J* 7.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 19.7, 29.1, 111.8, 119.6, 120.9, 123.1, 124.5, 127.3, 128.0, 128.4, 136.4; *m/z* LRMS (EI^+) 221 $[M+H]^+$ (12%), 220 $[M]^+$ (70%), 219 $[M]^+$ (65%), 218 [M-

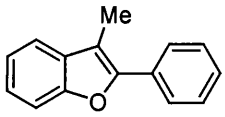
$H_2]^+$ (100%), 191 $[M\text{-}CO]^+$ (25%), 189 $[M\text{-}CO\text{-}H_2]^+$ (55%); (CI^+, NH_3) 221 $[M+H]^+$; HRMS (ES^+) calc. for $C_{16}H_{13}O$: 221.0961 $[M+H]^+$; found: 221.0959 $[M+H]^+$.

Preparation of **9-fluoro-5,6-dihydrobenzo[β]naphtha[2,1-δ]furan, 134**



General procedure C was followed employing *ketone* **133** (50 mg, 0.16 mmol), using sodium *tert*-butoxide (23 mg, 0.24 mmol) as the base and heating at 100 °C for 48 hours. The product was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *benzofuran* **134** (24 mg, 64%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3053, 2936, 1619, 1593, 1471, 1445, 1435, 1390, 1351, 1321, 1277, 1251, 1219, 1170, 1141, 1108, 1082, 1043, 1021, 958, 925, 883, 831, 800, 758, 728, 706, 680, 656, 599; δ_H (300 MHz, $CDCl_3$) 2.95 (2H, t, *J* 8.1, C=CCH_2), 3.13 (2H, t, *J* 8.1, Ar-CH_2), 6.99 (1H, td, *J* 8.9 and 2.5, Ar-*H*), 7.16 (1H, dd, *J* 8.9 and 2.5, Ar-*H*), 7.21-7.37 (3H, m, Ar-*H*), 7.45 (1H, dd, *J* 7.8 and 4.1, Ar-*H*), 7.67 (1H, d, *J* 7.8, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 19.6, 28.9, 105.0, 105.8, 111.8 (d, J_{CF} 26.4), 112.3 (d, J_{CF} 9.0), 114.0, 121.1, 127.3, 128.4, 128.5, 129.6, 136.5, 154.0, 158.2; *m/z* LRMS (EI^+) 239 $[M+H]^+$ (14%), 238 $[M]^+$ (100%), 237 $[M-H]^+$ (71%), 209 [M-CHO] (33%), 207 $[M\text{-}CH_3O]^+$ (28%); (CI^+, NH_3) 239 $[M+H]^+$; HRMS (ES^+) calc. for $C_{16}H_{15}FNO$: 239.0867 $[M+NH_4]^+$; found: 239.0865 $[M+NH_4]^+$.

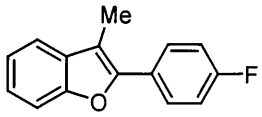
Preparation of **3-methyl-2-phenylbenzofuran, 140**



General procedure C was followed employing ketone **139** (100 mg, 0.35 mmol), using sodium *tert*-butoxide (48 mg, 0.52 mmol) as the base and heating at 80 °C for 23 hours. The product was purified *via* flash column chromatography (petrol) to yield *benzofuran* **140** (50 mg, 70%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3060, 2923, 1494, 1456, 1420, 1344, 1260, 1213, 1137, 1114, 1069, 1006, 766, 744, 693; δ_H (300 MHz, $CDCl_3$) 2.49 (3H, s, CH_3), 7.23-7.33 (2H, m, Ar-*H*), 7.36 (1H, tt, *J* 7.5 and 1.9, Ar-*H*), 7.45-7.57 (4H, m, Ar-*H*), 7.82 (2H, d, *J* 8.3, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 9.9, 111.3, 111.6, 119.6, 122.7, 124.7, 127.1, 128.3, 128.5, 129.0, 130.1, 131.6, 131.8, 151.1, 154.2; *m/z* LRMS

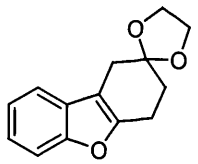
(EI$^+$) 209 $[M+H]^+$ (15%), 208 $[M]^+$ (100%), 207 $[M-H]^+$ (66%), 178 $[M-CH_2O]^+$ (47%) 131 $[M-C_4H_8O]^+$ (28%); (CI$^+$, NH_3) 209 $[M+H]^+$; HRMS (ES$^+$) calc. for $C_{15}H_{16}NO$: 209.0961 $[M+NH_4]^+$; found: 209.0961 $[M+NH_4]^+$.

Preparation of **2-(4-fluorophenyl)-3-methylbenzofuran, 142**



General procedure C was followed employing *ketone* **141** (100 mg, 0.33 mmol), using sodium *tert*-butoxide (47 mg, 0.49 mmol) as the base and heating at 100 °C for 22 hours. The product was purified *via* flash column chromatography (petrol) to yield *benzofuran* **142** (35 mg, 48%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3062, 2922, 2868, 1604, 1584, 1507, 1476, 1454, 1410, 1386, 1347, 1292, 1258, 1233 (w), 1158, 1115, 1090, 1006, 878, 836, 789, 744; δ_H (300 MHz, $CDCl_3$) 2.37 (3H, s, C*H*$_3$), 7.09 (2H, app. tt, *J* 8.8 and 2.3, Ar-*H*), 7.15-7.25 (2H, m, Ar-*H*), 7.38-7.48 (2H, m, Ar-*H*), 7.70 (1H, dd, *J* 9.0 and 5.3, Ar-*H*), 7.67-7.74 (1H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$); 9.8, 111.3, 116.1 (d, J_{CF} 21.7), 119.7, 122.8, 124.8, 128.0 (d, J_{CF} 3.1), 128.9 (d, J_{CF} 8.1), 131.2, 150.3, 154.1, 161.1, 164.4; *m/z* LRMS (EI$^+$) 227 $[M+H]^+$ (13%), 226 $[M]^+$ (91%), 225 $[M-H]^+$ (56%), 196 $[M-CH_2O]^+$ (26%); (CI$^+$, NH_3) 227 $[M+H]^+$ 226 $[M]^+$; HRMS (ES+) calc. for $C_{15}H_{12}FO$: 227.0867 $[M+H]^+$; found: 227.0865 $[M+H]^+$.

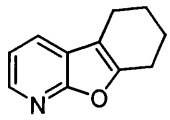
Preparation of **3,4-dihydro-*1H*-dibenzofuran-2-one ethylene ketal, 144**



General procedure C was followed employing *ketone* **143** (50 mg, 0.16 mmol), using sodium *tert*-butoxide (23 mg, 0.24 mmol) as the base and heating at 100 °C for 17 hours. The product was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *benzofuran* **144** (23 mg, 63%) as a creamy coloured solid. ν_{max} (KBr)/cm^{-1} 2922, 2889, 1639, 1609, 1480, 1454, 1439, 1372, 1339, 1295, 1279, 1263, 1232, 1208, 1178, 1126, 1098, 1058, 1022, 950, 882, 848, 826, 758, 697; δ_H (300 MHz, $CDCl_3$) 2.10 (2H, t, *J* 6.5, CC*H*$_2$CH$_2$), 2.89 (2H, s, CC*H*$_2$C=C), 2.95 (2H, tt, *J* 6.5 and 1.5, C*H*$_2$CO=C), 4.01-4.12 (4H, m, O(C*H*$_2$)$_2$O), 7.15-7.24 (2H, m, Ar-*H*), 7.34-7.43 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 22.1, 31.9, 32.0, 65.2, 108.9, 111.3, 111.5, 118.67,

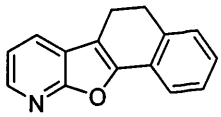
122.6, 123.7, 129.0, 152.8, 155.7; *m/z* LRMS (EI^+) 230 $[M]^+$ (32%), 144 $[M-C_3H_2O_3]^+$ (100%); (CI^+, NH_3) 249 $[M+NH_4]^+$, 248 $[M+NH_3]^+$, 231 $[M+H]^+$, 230 $[M]^+$; HRMS (ES^+) calc. for $C_{14}H_{18}NO_3$: 248.1281 $[M+NH_4]^+$; found: 248.1279 $[M+NH_4]^+$.

Preparation of **5,6,7,8-tetrahydro-benzo[4,5]furo[2,3-*β*]pyridine, 146**



General procedure C was followed employing *ketone* **145** (50 mg, 0.24 mmol), using sodium *tert*-butoxide (34 mg, 0.36 mmol) as the base and heating at 100 °C for 20 hours. The product was purified *via* flash column chromatography (petrol) to yield *benzofuran* **146** (18 mg, 45%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3054, 2933, 2848, 1637, 1586, 1447, 1407, 1393, 1363, 1299, 1256, 1233, 1181, 1117, 991, 791, 776; δ_H (300 MHz, $CDCl_3$) 1.83-2.04 (4H, m, C*H*$_2$), 2.59-2.69 (2H, m, C*H*$_2$C=CO), 2.76-2.86 (2H, m, C*H*$_2$CO=C), 7.17 (1H, dd, *J* 7.5 and 4.8, Ar-*H*), 7.74 (1H, dd, *J* 7.5 and 1.5, Ar-*H*), 8.22 (1H, dd, *J* 4.8 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 20.5, 22.7, 22.9, 23.5, 112.5, 118.8, 121.2, 127.1, 142.6, 154.4, 161.9; *m/z* LRMS (EI^+) 174 $[M+H]^+$ (5%), 173 $[M]^+$ (39%), 172 $[M-H]^+$ (13%), 145 $[M-CO]^+$ (100%); (CI^+, NH_3) 174 $[M]^+$, 175 $[M+H]^+$; HRMS (ES^+) calc. for $C_{11}H_{15}N_2O$: 174.0913 $[M+NH_4]^+$; found: 174.0913 $[M+NH_4]^+$.

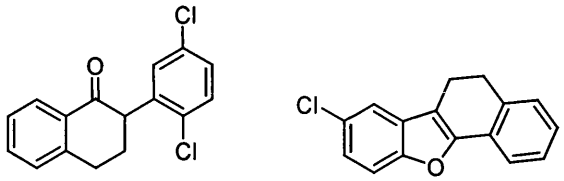
Preparation of **1-pyridyl-5,6-dihydro-*2H*-benzo[*β*]naphtha[9,10-δ]furan, 148**



General procedure B was followed employing 3-bromo-2-chloropyridine (160 mg, 0.83 mmol) and α-tetralone (146 mg, 0.10 mmol, 0.13 mL) using sodium *tert*-butoxide (120 mg, 1.25 mmol) as the base, heating at 110 °C for 24 hours. The product was purified *via* flash column chromatography (10% diethyl ether:petrol) to yield *benzofuran* **148** (179 mg, 83%) as a yellow oil. ν_{max} (film)/cm^{-1} 3053, 2936, 2832, 1916, 1847, 1619, 1593, 1471, 1455, 1435, 1418, 1390, 1351, 1321, 1277, 1251, 1219, 1170, 1141, 1108, 1082, 1043, 1021, 958, 925, 883, 831, 800, 758, 728, 706, 687, 656; δ_H (300 MHz, $CDCl_3$) 2.87 (2H, td, *J* 8.3 and 1.5, C*H*$_2$C=C), 3.04 (2H, t, *J* 8.3, Ar-C*H*$_2$), 7.11-7.28 (4H, m, Ar-*H*), 7.66 (1H, d, *J* 7.5, Ar-*H*), 7.73 (1H, dd, *J* 7.5 and 1.5, Ar-*H*),

8.19 (1H, dd, *J* 4.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 19.2, 28.6, 113.2, 119.5, 121.1, 121.7, 127.1, 127.3, 128.1, 128.5, 128.8, 136.4, 143.7, 151.8, 162.7; *m/z* LRMS (CI^+, NH_3) 222 $[M+H]^+$, 220 $[M-H]^+$; HRMS (ES^+) calc. for $C_{15}H_{12}NO$: 222.0913 $[M+H]^+$; found: 222.0913 $[M+H]^+$.

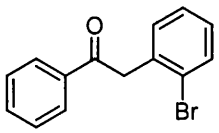
Preparation of **2-(2,5-dichlorophenyl)-3,4-dihydro-*2H*-naphthalen-1-one, 135; 8-chloro-5,6-dihydrobenzo[β]naphtho[2,1-δ]furan, 136**

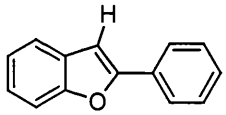


General procedure D was followed employing 1-bromo-2,5-dichlorobenzene (160 mg, 0.71 mmol) and α-tetralone (121 mg, 0.85 mmol, 0.11 mL), heating at 110 °C for 24 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:hexane) to yield a mixture of products **135** and **136**. *Ketone* **135** (47 mg, 23%) as a white crystalline solid: mp 98-100 °C. ν_{max} (KBr)/cm^{-1} 3060, 3018, 2943, 1683, 1597, 1467, 1453, 1437, 1390, 1354, 1296, 1263, 1221, 1154, 1096, 1035, 1012, 966, 909, 878, 817, 753; δ_H (300 MHz, $CDCl_3$) 2.22-2.49 (2H, m, ArCHCH_2), 3.08 (1H, dt, *J* 16.7 and 3.8, Ar-CH_2), 3.23 (1H, ddd, *J* 16.7, 12.4 and 4.6, Ar-CH_2), 4.24 (1H, dd, *J* 12.4 and 4.6, Ar-C*H*), 7.19 (1H, dd, *J* 3.5 and 0.9, Ar-*H*), 7.22 (1H, d, *J* 2.6, Ar-*H*), 7.31 (1H, d, *J* 7.5, Ar-*H*), 7.35 (1H, dd, *J* 8.1 and 0.9, Ar-*H*), 7.37 (1H, d, *J* 7.5, Ar-*H*), 7.53 (1H, td, *J* 7.5 and 1.5, Ar-*H*), 8.10 (1H, dd, *J* 8.1 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 29.9, 30.4, 52.5, 127.3, 128.3, 128.8, 129.2, 130.0, 131.0, 133.0, 133.2, 134.1, 140.0, 144.1, 196.6; *m/z* LRMS (CI^+, NH_3) 312 $[M+NH_3{:}^{37}Cl]^+$, 310 $[M+NH_3{:}^{35/37}Cl]^+$, 308 $[M+NH_3{:}^{35}Cl]^+$, 293 $[M{:}^{37}Cl]^+$, 291 $[M{:}^{35}Cl]^+$, 276 $[M\text{-}OH{:}^{37}Cl]^+$, 274 $[M\text{-}OH{:}^{35}Cl]^+$; HRMS ($ES^+$) calc. for $C_{16}H_{16}Cl_2NO$: 308.0603 $[M+NH_4]^+$; found: 308.0600 $[M+NH_4]^+$. *Benzofuran* **136** (30 mg, 17%) as a white crystalline solid: mp 91-92 °C. ν_{max} (Nujol™)/cm^{-1} 2915, 2841, 1456, 1431, 1329, 1310, 1222, 1245, 1181, 1144, 1093, 1061, 1042, 1019, 935, 846, 797, 762, 690; δ_H (300 MHz, $CDCl_3$) 2.92 (2H, td, *J* 7.9 and 1.1, CH_2C=C), 3.10 (2H, t, *J* 7.9, Ar-CH_2), 7.19-7.34 (4H, m, Ar-*H*), 7.42 (1H, d, *J* 8.7, Ar-*H*), 7.46 (1H, d, *J* 2.6, Ar-*H*), 7.64 (1H, d, *J* 7.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 19.6, 28.9, 112.7, 114.0, 119.3, 121.1, 124.4, 127.3, 127.7, 128.5, 128.8, 130.1, 136.5, 153.7, 154.0; *m/z* LRMS (EI^+) 256 $[M{:}^{37}Cl]^+$ (30%), 255 $[M+H{:}^{35}Cl]^+$ (28%), 254 $[M{:}^{35}Cl]^+$ (100%), 253 $[M\text{-}H{:}^{35}Cl]^+$ (45%), 218 $[M\text{-}Cl]^+$ (52%), 189 $[M\text{-}CHOCl]^+$

(32%); (CI^+, NH_3) 257 $[M+H:^{37}Cl]^+$, 255 $[M+H:^{35}Cl]^+$, 254 $[M]^+$; HRMS (EI^+) calc. for $C_{16}H_{11}ClO$: 254.0493 $[M]^+$; found: 254.0493 $[M]^+$.

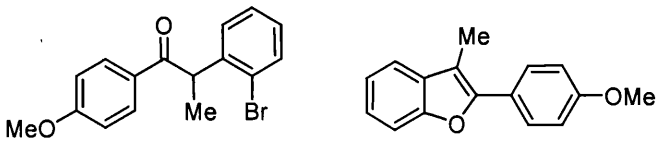
Preparation of **2-(2-bromophenyl)-1-phenylethanone, 137; 2-phenylbenzofuran, 138**





General procedure D was followed employing 1-bromo-2-iodobenzene (200 mg, 0.71 mmol, 0.09 mL) and acetophenone (100 mg, 0.85 mmol, 0.10 mL), heating at 110 °C for 24 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:heptane) to yield a mixture of products **137** and **138**. *Ketone* **137** (144 mg, 74%) as a white crystalline solid: mp 66-67 °C. ν_{max} (Nujol™)/cm^{-1} 3057, 1691, 1585, 1581, 1567, 1470, 1447, 1427, 1407, 1331, 1277, 1219, 1202, 1174, 1156, 1025, 990, 756, 690, 666, 650, 575; δ_H (300 MHz, $CDCl_3$) 4.46 (2H, s, Ar-C*H*$_2$CO), 7.15 (1H, ddd, *J* 8.0, 6.8 and 2.3, Ar-*H*), 7.22-7.32 (2H, m, Ar-*H*), 7.47 (2H, tt, *J* 8.0 and 1.5, Ar-*H*), 7.55-7.62 (2H, m, Ar-*H*), 8.05 (2H, d, *J* 7.2, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 45.8, 125.1, 127.5, 128.3, 128.7, 131.7, 132.8, 133.3, 133.8, 134.9, 136.6, 196.3; *m/z* LRMS (CI^+, NH_3) 294 $[M+NH_4:^{81}Br]^+$, 292 $[M+NH_4:^{79}Br]^+$, 277 $[M+NH_3:^{81}Br]^+$, 275 $[M+NH_3:^{79}Br]^+$; HRMS (ES^+) calc. for $C_{14}H_{15}BrNO$: 292.0332 $[M+NH_4:^{79}Br]^+$; found: 292.0331 $[M+NH_4:^{79}Br]^+$. *Benzofuran* **138** (32 mg, 23%) as a white crystalline solid: 115-116 °C. ν_{max} (Nujol™)/cm^{-1} 3035, 1492, 1563, 1471, 1456, 1442, 1260, 1208, 1039, 1021, 920, 806, 739, 763, 747, 690; δ_H (300 MHz, $CDCl_3$) 6.95 (1H, d, *J* 1.1, C=C*H*), 7.15 (1H, td, *J* 7.2 and 1.3, Ar-*H*), 7.21 (1H, td, *J* 7.2 and 1.3, Ar-*H*), 7.25-7.31 (1H, m, Ar-*H*), 7.34-7.41 (2H, m, Ar-*H*), 7.43-7.45 (1H, m, Ar-*H*), 7.51 (1H, ddd, *J* 7.7, 1.9 and 0.9, Ar-*H*), 7.77-7.82 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 101.7, 111.6, 121.3, 123.4, 124.7, 125.3, 129.0, 129.2, 129.6, 130.9, 155.3, 156.3; *m/z* LRMS (EI^+) 195 $[M+H]^+$ (12%), 194 $[M]^+$ (100%), 165 $[M-CHO]^+$ (80%); (CI^+, NH_3) 195 $[M+H]^+$; HRMS (EI^+) calc. for $C_{14}H_{10}O$: 194.0726 $[M]^+$; found: 194.0727 $[M]^+$.

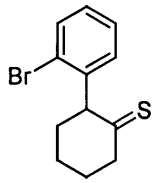
Preparation of **2-(2-bromophenyl)-1-(4-methoxyphenyl)-propan-1-one, 150; 2-(4-methoxyphenyl)-3-methylbenzofuran, 151**



General procedure D was followed employing 1-bromo-2-iodobenzene (200 mg, 0.71 mmol, 0.09 mL) and 4-methoxypropiophenone (139 mg, 0.85 mmol), heating at 110 °C for 24 hours. The product was purified *via* flash column chromatography (5 to 20% diethyl ether:petrol) to yield a mixture of products **150** and **151**. *Ketone* **150** (147 mg, 64%) as a yellow oil. ν_{max} (Nujol™)/cm^{-1} 3337, 3064, 2975, 2932, 2869, 2839, 1677, 1601, 1574, 1510, 1471, 1439, 1419, 1372, 1309, 1247, 1231, 1171, 1119, 1069, 1024, 952, 846, 796, 755, 695; δ_H (300 MHz, $CDCl_3$) 1.46 (3H, d, *J* 6.8, CHC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 5.06 (1H, q, *J* 6.8, COC*H*CH$_3$), 6.86 (1H, d, *J* 9.0, Ar-*H*), 6.86 (1H, dd, *J* 9.8 and 5.3, Ar-*H*), 7.03-7.09 (1H, m, Ar-*H*), 7.13 (1H, dd, *J* 7.9 and 2.3, Ar-*H*), 7.19 (1H, td, *J* 6.8 and 1.1, Ar-*H*), 7.59 (1H, dd, *J* 7.9 and 1.5, Ar-*H*), 7.92 (1H, d, *J* 9.0, Ar-*H*), 7.92 (1H, dd, *J* 9.8 and 4.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 18.4, 47.1, 55.8, 114.2, 124.2, 128.6, 128.8, 129.0, 129.4, 131.4, 133.6, 141.8, 163.7, 199.0; *m/z* LRMS (CI$^+$, NH_3) 338 [M+NH$_4$:^{81}Br]$^+$, 336 [M+NH$_4$:^{79}Br]$^+$, 321 [M+H:^{81}Br]$^+$, 319 [M+H:^{79}Br]$^+$, 239 [M-Br]$^+$, 135 [M-BrC$_7$H$_4$O]$^+$: HRMS (ES$^+$) calc. for $C_{16}H_{16}BrO_2$: 319.0328 [M+H:^{79}Br]$^+$; found: 319.0327 [M+H:^{79}Br]$^+$. *Benzofuran* **151** (60 mg, 36%) as a white crystalline solid: mp 40-42 °C. ν_{max} (Nujol™)/cm^{-1} 3061, 2929, 2836, 1612, 1510, 1455, 1476, 1441, 1419, 1298, 1251, 1214, 1177, 1114, 1094, 1038, 1019, 1001, 832, 779, 743; δ_H (300 MHz, $CDCl_3$) 2.44 (3H, s, C*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 7.02 (2H, dt, *J* 9.4 and 2.4, Ar-*H*), 7.21-7.31 (2H, m, Ar-*H*), 7.44-7.55 (2H, m, Ar-*H*), 7.75 (2H, dt, *J* 9.4 and 2.4, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 9.8, 55.8, 110.1, 111.2, 114.5, 119.4, 122.6, 124.3, 124.6, 128.6, 131.7, 151.2, 154.0, 159.8; *m/z* LRMS (EI$^+$) 239 [M+H]$^+$ (20%), 238 [M]$^+$ (100%), 223 [M-CH$_3$] (60%); HRMS (EI$^+$) calc. for $C_{16}H_{14}O_2$: 238.0994 [M]$^+$; found: 238.0993 [M]$^+$.

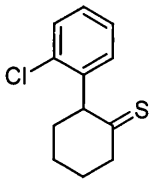
General Procedure E: Preparation of Thioketones

Preparation of **2-(2-bromophenyl)-cyclohexanethione, 154**



Ketone **111** (500 mg, 1.98 mmol) was added to a flask charged with phosphorus pentasulfide (220 mg, 0.49 mmol) under nitrogen and the reaction mixture suspended in anhydrous toluene (2.50 mL). The mixture was stirred at room temperature for 10 minutes prior to the addition of hexamethyldisiloxane (550 mg, 3.36 mmol, 0.71 mL) and heated to 90 °C for 21 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of silica and the filtrate reduced *in vacuo* to yield the *thioketone* **154** (375 mg, 71%) as a colourless oil. The product was used without further purification. ν_{max} (NaCl)/cm^{-1} 3050, 2924, 2855, 1642, 1587, 1559, 1466, 1435, 1334, 1258, 1243, 1136, 1115, 1078, 1050, 1027, 1014, 821, 799, 751, 724, 688; δ_H (300 MHz, $CDCl_3$) 1.63-1.80 (4H, m, C*H*$_2$), 1.95-2.12 (1H, m, ArCHC*H*$_2$), 2.24-2.38 (3H, m, ArCHC*H*$_2$ and C*H*$_2$CS), 2.39 (1H, s (br), Ar-C*H*), 7.03-7.10 (2H, m, Ar-*H*), 7.24 (1H, td, *J* 7.9 and 1.4, Ar-*H*), 7.53 (1H, dd, *J* 7.9 and 1.4, Ar-*H*); δ_C (75 MHz, $CDCl_3$); 23.2, 24.0, 32.0, 34.1, 123.4, 125.9, 128.2, 129.0, 130.6, 133.4, 133.7, 143.8; *m/z* LRMS (EI$^+$) 271 [M:^{81}Br]$^+$ (53%), 270 [M-H:^{81}Br]$^+$ (52%), 269 [M:^{79}Br]$^+$ (100%), 268 [M-H:^{79}Br]$^+$ (48%), 189 [M-Br]$^+$ (40%); (CI$^+$, NH_3) 288 [M+NH_3:^{81}Br]$^+$, 286 [M+NH_3:^{79}Br]$^+$, 272 [M$^+$H:^{81}Br]$^+$, 271 [M:^{81}Br]$^+$, 270 [M+H:^{79}Br]$^+$, 269 [M:^{79}Br]$^+$; HRMS (EI) calc. for $C_{12}H_{13}BrS$: 267.9916 [M]$^+$; found: 267.9917[M]$^+$.

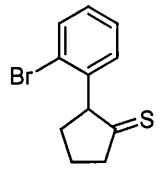
Preparation of **2-(2-chlorophenyl)-cyclohexanethione, 156**



General procedure E was followed employing *ketone* **123** (180 mg, 1.32 mmol) to yield *thioketone* **156** (80 mg, 40%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3645, 3055, 2925, 2857, 2833, 2661, 2571, 2318, 1799, 1722, 1643, 1590, 1564, 1470, 1428, 1335, 1260, 1174, 1121, 1078, 1059, 1034 1016, 941, 862, 801, 753, 728, 709, 650; δ_H (300 MHz, $CDCl_3$) 1.69-1.86 (4H, m, C*H*$_2$), 2.02-2.19 (2H, m, ArCHC*H*$_2$), 2.31-2.44 (2H, m,

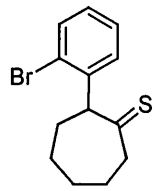
CH_2CS), 2.46 (1H, s (br), Ar-C*H*), 7.15 (1H, dd, *J* 7.2 and 2.3, Ar-*H*), 7.24 (1H, app. qd, *J* 7.2 and 2.3, Ar-*H*), 7.41 (1H, dd, *J* 7.2 and 2.3, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.1, 31.9, 34.2, 126.0, 127.5, 128.9, 130.2, 130.6, 132.2, 133.2, 141.8. *m/z* LRMS (EI^+) 224 $[M:^{35}Cl]^+$ (34%), 189 $[M-^{35}Cl]^+$ (100%), 188 $[M-H-^{35}Cl]^+$ (62%), 187 $[M-^{37}Cl]$ (33%); HRMS (ES^+) calc. for $C_{12}H_{14}ClS$: 225.0499 $[M+H]^+$; found: 225.0498 $[M+H]^+$.

Preparation of **2-(2-bromophenyl)-cyclopentanethione, 157**



General procedure E was followed employing *ketone* **119** (200 mg, 0.84 mmol) to yield *thioketone* **157** (80 mg, 38%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3062, 2923, 2848, 1742 (vs), 1634, 1559, 1467, 1429, 1317, 1262, 1204, 1115, 1057, 1028, 752, 722, 699; δ_H (300 MHz, $CDCl_3$) 1.93-2.05 (2H, m, CH_2), 2.57-2.71 (5H, m, Ar-C*H*, ArCHCH_2 and CH_2CS), 7.04-7.14 (2H, m, Ar-*H*), 7.21-7.27 (1H, m, Ar-*H*), 7.53 (1H, dd, *J* 7.9 and 0.8, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 27.4, 29.0, 30.2, 121.8, 123.5, 123.7, 124.2, 135.7, 141.2, 143.4, 145.5; *m/z* LRMS (EI^+) 256 $[M+H:^{79}Br]^+$ (95%), 254 $[M-H:^{79}Br]^+$ (100%); (CI^+, NH_3) 272 $[M+NH_3:^{79}Br]^+$, 258 $[M+H:^{81}Br]^+$, 257 $[M:^{81}Br]^+$, 256 $[M+H:^{79}Br]^+$, 255 $[M:^{79}Br]^+$, 254 $[M-H:^{79}Br]^+$; HRMS (EI) calc. for $C_{11}H_{11}BrS$: 253.9759 $[M]^+$; found: 253.9756 $[M]^+$.

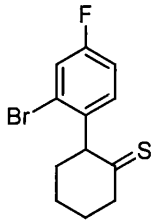
Preparation of **2-(2-bromophenyl)-cycloheptanethione, 159**



General procedure E was followed employing *ketone* **127** (430 mg, 1.62 mmol) to yield *thioketone* **159** (181 mg, 40%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3049, 2923, 2848, 2569, 1630, 1587, 1558, 1466, 1446, 1432, 1356, 1343, 1269, 1148, 1026, 979, 750, 726, 685; δ_H (300 MHz, $CDCl_3$) 1.61-1.90 (5H, m, CH_2), 2.27-2.69 (5H, m, ArCHCH_2, CH_2CS and CH_2), 2.70 (1H, s (br), Ar-C*H*), 7.08-7.17 (2H, m, Ar-*H*), 7.30 (1H, app. td, *J* 7.2 and 1.5, Ar-*H*), 7.61 (1H, app. dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 26.6, 26.8, 32.1, 35.9, 38.5, 122.9, 128.3, 128.7, 130.4, 131.0, 133.5, 137.3,

146.3; *m/z* LRMS (EI^+) 284 $[M:^{81}Br]^+$ (12%), 282 $[M:^{79}Br]^+$ (12%), 203 $[M\text{-}Br]^+$ (52%), 202 $[M\text{-}^{81}Br]^+$ (54%), 201, 173, 160, 147; (CI^+, NH_3) 300 $[M+NH_3]^+$, 286 $[M+H_2:^{81}Br]^+$, 285 $[M+H:^{81}Br]^+$, 284 $[M:^{81}Br]^+$, 283 $[M+H:^{79}Br]^+$, 204 $[M\text{-}^{79}Br]^+$, 203 $[M+H\text{-}^{81}Br]^+$, 202 $[M\text{-}^{81}Br]^+$, 201 $[M\text{-}H\text{-}^{81}Br]^+$; HRMS (EI) calc. for $C_{13}H_{15}BrS$: 282.0072 $[M:^{79}Br]^+$; found: 282.0072 $[M:^{79}Br]^+$.

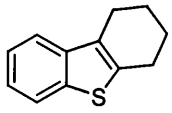
Preparation of **2-(4-fluoro-2-bromophenyl)-cyclohexanethione, 161**



General procedure E was followed employing *ketone* **129** (200 mg, 0.74 mmol) to yield *thioketone* **161** (113 mg, 53%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 2962, 2932, 2858, 2833, 1715, 1644, 1596, 1577, 1483, 1446, 1384, 1336, 1260, 1198, 1016, 872, 815, 666; δ_H (300 MHz, $CDCl_3$) 1.70-1.88 (4H, m, CH_2), 2.00-2.14 (1H, m, $ArCHCH_2$), 2.41-2.27 (3H, m, $ArCHCH_2$ and CH_2CS), 2.43 (1H, s, Ar-C*H*), 7.03 (1H, td, *J* 8.4 and 2.5, Ar-*H*), 7.11 (1H, dd, *J* 8.4 and 6.2, Ar-*H*), 7.35 (1H, dd, *J* 8.4 and 2.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.0, 32.1, 34.2, 115.4 (d, J_{CF} 24.2), 126.9, 120.5 (d, J_{CF} 21.1), 131.5 (d, J_{CF} 8.1), 132.8, 139.8 (d J_{CF} 3.7), 160.1, 163.5; *m/z* LRMS (EI^+) 288 $[M:^{81}Br]$ (87%), 286 $[M:^{79}Br]$ (100%); (CI^+, NH_3) 208 $[M\text{-}^{79}Br]^+$, 207 $[M+H\text{-}^{79}Br]^+$, 206 $[M\text{-}^{81}Br]^+$, 205 $[M\text{-}H\text{-}^{81}Br]^+$; HRMS (EI) calc. for $C_{12}H_{12}BrFS$: 285.9822 $[M:^{79}Br]^+$; found: 285.9826 $[M:^{79}Br]^+$.

General Procedure F: Preparation of Benzothiophenes by Palladium Catalysis

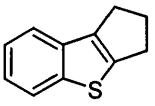
Preparation of **1,2,3,4-tetrahydro-dibenzothiophene, 155**



Cesium carbonate (180 mg, 0.56 mmol) was added to a flask charged with $Pd_2(dba)_3$ (9 mg, 0.01 mmol) and DPEphos (13 mg, 0.02 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.5 mL) prior to the addition of *thioketone* **154** (100 mg, 0.37 mmol) and the reaction heated to 100 °C for 20 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of celite and the filtrate reduced *in vacuo*. The residue was purified *via* flash column

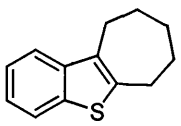
chromatography (petrol) to yield *benzothiophene* **155** (52 mg, 74%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3058, 2933, 2855, 2838, 1580, 1461, 1445, 1349, 1300, 1250, 1151, 1124, 1066, 1024, 966, 950, 931, 848, 819, 804, 750, 728, 714; δ_H (300 MHz, $CDCl_3$) 1.87-1.99 (4H, m, C*H*$_2$), 2.72-2.79 (2H, m, C*H*$_2$C=CS), 2.84-2.90 (2H, m, C*H*$_2$CS=C), 7.22-7.36 (2H, m, Ar-*H*), 7.57 (1H, dd, *J* 7.2 and 1.1, Ar-*H*), 7.76 (1H, d, *J* 7.2, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 22.7, 24.0, 24.1, 26.1, 120.8, 122.6, 123.9, 124.2, 129.9, 137.1, 138.8, 140.2; *m/z* LRMS (EI$^+$) 188 [M]$^+$ (100%), 187 [M-H]$^+$ (60%); (CI$^+$, NH_3) 189 [M+H]$^+$, 188 [M]$^+$, 187 [M-H]$^+$; HRMS (EI) calc. for $C_{12}H_{11}S$: 187.0576 [M-H]$^+$; found: 187.0570 [M-H]$^+$. Data are in agreement with literature values.[17,18]

Preparation of **2,3-dihydro-*1H*-benzo(β)cyclopenta(δ)thiophene, 158**



General procedure F was followed employing *thioketone* **157** (50 mg, 0.20 mmol) to yield *benzothiophene* **158** (15 mg, 44%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3058, 2923, 2851, 1699, 1571, 1467, 1428, 1378, 1319, 1296, 1258, 1152, 1066, 1017, 800, 750, 728; δ_H (300 MHz, $CDCl_3$) 2.51-2.62 (2H, m, C*H*$_2$), 2.86-2.93 (2H, m, C*H*$_2$C=CS), 2.98-3.07 (2H, m, C*H*$_2$CS=C), 7.24 (1H, td, *J* 7.5 and 1.3, Ar-*H*), 7.32 (1H, td, *J* 7.5 and 1.3, Ar-*H*), 7.56 (1H, d, *J* 7.5, Ar-*H*), 7.76 (1H, dt, *J* 7.5 and 1.3, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 27.4, 29.0, 30.2, 121.8, 123.5, 123.7, 124.2, 135.7, 141.2, 143.4, 145.5; *m/z* LRMS (EI$^+$) 174 [M]$^+$ (18%), 173 [M-H]$^+$ (39%); (CI$^+$, NH_3) 173 [M]$^+$; HRMS (EI) calc. for $C_{11}H_9S$: 173.0419 [M-H]$^+$; found: 173.0415 [M-H]$^+$.

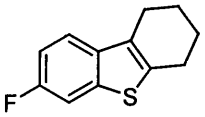
Preparation of **6,7,8,9-tetrahydro-*5H*-10-oxa-benzothiazulene, 160**



General procedure F was followed employing *thioketone* **159** (100 mg, 0.37 mmol) to yield *benzothiophene* **160** (41 mg, 52%) as a yellow solid: mp 65-66 °C. ν_{max} (NaCl)/cm^{-1} 3059, 2921, 2838, 1442, 1435, 1359, 1311, 1262, 1223, 1151, 1090, 1019, 823, 800, 750, 725, 667; δ_H (300 MHz, $CDCl_3$) 1.68-1.82 (4H, m, C*H*$_2$), 1.90-1.99 (2H, m, C*H*$_2$), 2.87-2.96 (4H, m, C*H*$_2$C=CS and C*H*$_2$CS=C), 7.25 (1H, td, *J* 7.9 and 1.1, Ar-*H*), 7.34 (1H, td, *J* 7.9 and 1.1, Ar-*H*), 7.62 (1H, d, *J* 7.9, Ar-*H*), 7.75 (1H, dt, *J* 7.9 and

1.1, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 26.0, 26.8, 28.7, 29.3, 31.3, 119.8, 121.1, 122.1, 122.6, 133.2, 137.0, 139.6, 139.9; *m/z* LRMS (EI^+) 202 $[M]^+$ (100%), 173 $[M-C_2H_5]$ (90%), 160 $[M-C_3H_6]$ (45%), 147 $[M-C_4H_7]^+$ (58%); (CI^+, NH_3) 203 $[M+H]^+$, 202 $[M]^+$; HRMS (EI) calc. for $C_{13}H_{14}S$: 202.0811 $[M]^+$; found: 202.0810 $[M]^+$.

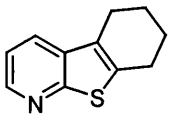
Preparation of **8-fluoro-1,2,3,4-tetrahydro-dibenzothiophene, 162**



General procedure F was followed employing *thioketone* **161** (100 mg, 0.37 mmol) to yield *benzothiophene* **162** (43 mg, 57%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3063, 2932, 2857, 2840, 1603, 1556, 1470, 1446, 1401, 1376, 1349, 1338, 1314, 1298, 1250, 1201, 1150, 1136, 1111, 1069, 1050, 1022, 979, 951, 894, 848, 822, 804, 790, 701, 600, 534; δ_H (300 MHz, $CDCl_3$) 1.85-1.98 (4H, m, C*H*$_2$), 2.69-2.77 (2H, m, C*H*$_2$C=CS), 2.80-2.87 (2H, m, C*H*$_2$CS=C), 7.07 (1H, td, *J* 8.9 and 2.4, Ar-*H*), 7.42-7.51 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 22.6, 23.9, 26.0, 30.1, 108.9 (d, J_{CF} 25.4), 112.8 (d, J_{CF} 23.6), 121.5 (d, J_{CF} 8.7), 129.4, 136.7, 137.0, 159.0, 162.1; *m/z* LRMS (EI^+) 206 $[M]^+$ (73%), 205 $[M-H]^+$ (24%), 178 $[M-C_2H_4]^+$ (100%); (CI^+, NH_3) 207 $[M+H]^+$, 206 $[M]^+$; HRMS (EI) calc. for $C_{12}H_{11}FS$: 206.0560 $[M]^+$; found: 206.0561 $[M]^+$.

Preparation of a Benzothiophene Without Palladium Catalysis

Preparation of **5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3,β]pyridine, 164**

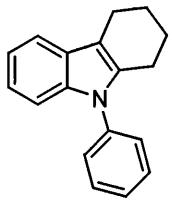


Ketone **145** (200 mg, 0.74 mmol) was added to a flask charged with phosphorus pentasulfide (82 mg, 0.18 mmol) under nitrogen and the reaction mixture suspended in anhydrous toluene (0.74 mL). The mixture was stirred at room temperature for 10 minutes prior to the addition of hexamethyldisiloxane (204 mg, 1.25 mmol, 0.27 mL) and heated to 90 °C for 18 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of silica and the filtrate reduced *in vacuo*. The residue was purified *via* flash column chromatography (petrol) to yield *benzothiophene* **164** (113 mg, 57%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3047, 2924, 2855, 2359, 1728, 1584, 1537, 1456, 1392, 1368, 1350, 1336, 1304, 1261, 1240, 1218,

1156, 1136, 1122, 1094, 1069, 1023, 972, 950, 848, 791, 748, 733, 672; δ_H (300 MHz, $CDCl_3$) 1.87-2.01 (4H, m, C*H*$_2$), 2.69-2.77 (2H, m, C*H*$_2$C=CS), 2.84-2.93 (2H, m, C*H*$_2$CS=C), 7.25 (1H, dd, *J* 7.9 and 4.9, Ar-*H*), 7.81 (1H, dd, *J* 7.9 and 1.5, Ar-*H*), 8.46 (1H, d, *J* 3.8, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 22.6, 23.6, 26.1, 30.1, 119.4, 127.7, 128.2, 138.2, 145.6, 161.2; *m/z* LRMS (EI^+) 189 $[M]^+$ (65%), 161 $[M-C_2H_4]$ (100%); (CI^+, NH_3) 190 $[M+H]^+$; HRMS (ES^+) calc. for $C_{11}H_{12}NS$: 190.0685 $[M+H]^+$; found: 190.0686 $[M+H]^+$.

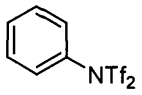
Palladium catalysed C-N bond formation

Preparation of **6,7,8,9-tetrahydro-9-phenyl-*5H*-carbazole, 113**



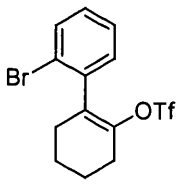
Ketone **111** (100 mg, 0.39 mmol) was added to a flask charged with 4Å MS under nitrogen. Toluene (0.40 mL) was added prior to the addition of aniline (40 mg, 0.44 mmol, 0.04 mL) and the mixture heated to 110 °C for 18 hours. The resulting crude imine (95% conv.) was transferred by filter cannular, under nitrogen, to a second flask charged with $Pd_2(dba)_3$ (9 mg, 0.01 mmol), DPEphos (13 mg, 0.02 mmol) and cesium carbonate (193 mg, 0.59 mmol). The flask was washed with a second aliquot of toluene (0.40 mL) and the reaction mixture heated for a further 24 hours at 100 °C. The mixture was cooled, filtered through a plug of celite with diethyl ether, reduced *in vacuo* and purified *via* flash column chromatography (hexane) to yield carbazole **113** (19 mg, 20%) as a colourless oil. crude imine **167**: δ_H (300 MHz, $CDCl_3$) 1.12-1.59 (4H, m, C*H*$_2$), 1.74-1.85 (1H, m, ArCHC*H*$_2$), 1.91-2.04 (2H, m, ArCHC*H*$_2$ and C*H*$_2$CN), 2.24-2.34 (1H, m, C*H*$_2$CN), 3.93 (1H, dd, *J* 12.8 and 5.3, Ar-C*H*), 6.71 (1H, ddd, *J* 7.9, 7.2 and 1.9, Ar-*H*), 6.98 (1H, td, *J* 7.2 and 1.3, Ar-*H*), 7.05 (1H, dd, *J* 7.9 and 1.9, Ar-*H*), 7.41 (1H, dd, *J* 8.3 and 1.3, Ar-*H*); carbazole **113**: δ_H (300 MHz, $CDCl_3$) 1.78-1.88 (4H, m, C*H*$_2$), 2.50-2.58 (2H, m, C*H*$_2$C=CN), 2.69-2.76 (2H, m, C*H*$_2$CN=C), 7.00-7.08 (2H, m, Ar-*H*), 7.12-7.18 (1H, m, Ar-*H*), 7.27-7.36 (3H, m, Ar-*H*), 7.40-7.48 (3H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 20.1, 22.0, 22.2, 22.3, 54.5, 108.7, 109.9, 113.1, 116.6, 113.3, 120.0, 126.4, 127.5, 129.7, 135.1, 136.5, 157.5. Data are in agreement with literature values.[19]

Preparation of ***N*-Phenyl-*bis*(trifluoromethanesulfonimide), 211**



A solution of trifluoromethanesulphonic anhydride (31.11 g, 0.11 mol, 18.55 mL) in anhydrous DCM (75 mL) was added dropwise to a solution of aniline (4.89 g, 0.05 mol, 4.79 mL) and triethylamine (11.69 g, 0.12 mol, 16.10 mL) in anhydrous DCM (75 mL) at -78 °C under nitrogen. The reaction was then allowed to slowly warm up to room temperature over 18 hours. The reaction mixture was quenched with saturated aqueous Na_2CO_3 solution (50 mL) and the product extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was filtered through a plug of silica (10% diethyl ether:petrol), the filtrate reduced *in vacuo* and the product recrystallised from DCM/hexane to yield *triflimide* **211** (11.63 g, 62%) as white needles: mp 102-103 °C (93-94 °C); ν_{max} (Nujol™)/cm^{-1} 2922, 1595 (w), 1495, 1481, 1377, 1246, 1228, 1120, 949, 894, 693, 606; δ_H (300 MHz, $CDCl_3$) 7.41 (2H, d, *J* 7.9, Ar-*H*), 7.48-7.63 (3H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 119.76 (q, J_{CF} 327.6), 130.35, 131.35, 132.31, 132.49. Data are in agreement with literature values.[20]

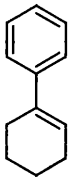
Preparation of **2-(2-bromophenyl)-cyclohexen-1-yl trifluoromethanesulfonate, 112**



A solution of ketone **111** (400 mg, 1.58 mmol) in anhydrous DMF (1 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 120 mg, 3.00 mmol) in anhydrous DMF (4 mL) cooled to 0 °C under nitrogen. The mixture was stirred for 3 hours at 0 °C, before the addition of *N*-phenyl-*bis*(trifluoromethanesulfonimide) (850 mg, 2.37 mmol) in one portion to the resultant yellow solution. The reaction was allowed to warm to room temperature and stirred over 18 hours. The reaction mixture was quenched with saturated aqueous Na_2CO_3 solution (10 mL) and the product extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with water (20 mL) and brine (2 × 25 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The residue was taken up in the miniumum volume of hexane (10 mL) and the excess triflating reagent was filtered off.

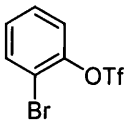
The filtrate was reduced *in vacuo* and purified *via* flash column chromatography (1 % diethyl ether: petrol) to yield *triflate* **112** (450 mg, 74%) as a colourless oil. ν_{max} (film)/cm^{-1} 2944, 2885, 1696 (w), 1590 (w), 1563 (w), 1471, 1414, 1246, 1246, 1211, 1140, 1080, 1034, 992, 891, 850, 809, 746, 619, 601; δ_H (300 MHz, $CDCl_3$) 1.74-1.85 (2H, m, C*H*$_2$), 1.85-1.96 (2H, m, C*H*$_2$), 2.20-2.33 (1H, m, ArCC*H*$_2$) 2.44-2.64 (3H, m, ArCC*H*$_2$ and C*H*$_2$C=CAr), 7.15-7.21 (2H, m, Ar-*H*), 7.32 (1H, ddd, *J* 7.9, 7.2 and 1.2, Ar-*H*), 7.57-7.61 (1H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 22.1, 23.3, 28.0, 30.9, 118.4 (q, J_{CF} 320.4), 122.7, 127.8, 129.8, 130.4, 131.5, 133.2, 138.1, 144.8; *m/z* HRMS (ES$^+$) calc. for $C_{13}H_{16}BrF_3SNO_3$: 401.9981 $[M+NH_4]^+$; found: 401.9986 $[M+NH_4]^+$; $C_{13}H_{12}BrF_3SO_3$ requires C 40.53, H 3.14%, found C 40.83, H 3.25%.

Preparation of **1-cyclohexenylbenzene, 195**



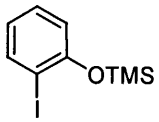
Triflate **X** (50 mg, 0.13 mmol) was added, as a solution in dioxane (0.5 mL), to a flask charged with $Pd_2(dba)_3$ (6 mg, 0.01 mmol), $HP^tBu_3BF_4$ (5 mg, 0.016 mmol) and sodium *tert*-butoxide (37 mg, 0.39 mmol) under nitrogen. Trimethylsilylethanol (31 mg, 0.26 mmol, 0.04 mL) was added and the mixture heated to 100 °C for 15 hours. The reaction mixture was cooled, diluted with diethyl ether and filtered through celite. The filtrate was reduced *in vacuo* and purified by flash column chromatography (petrol) to yield *alkene* **195** (17 mg, 77%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 1.62-1.72 (2H, m, C*H*$_2$), 1.74-1.84 (2H, m, C*H*$_2$), 2.17-2.27 (2H, m, ArCC*H*$_2$), 2.38-2.46 (2H, m, C*H*$_2$C=CAr), 6.02-6.07 (1H, m, C=C*H*), 7.18-7.24 (1H, m, Ar-*H*), 7.27-7.34 (2H, m, Ar-*H*), 7.36-7.41 (2H, m, Ar-*H*). Data are in agreement with literature values.[21]

Preparation of **1-bromo-2-trifluoromethanesulfonate-benzene**



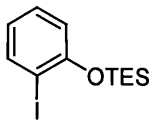
Pyridine (1.83 g, 23.12 mmol, 1.87 mL) was added dropwise to a solution of 2-bromophenol (2.00 g, 11.56 mmol, 1.34 mL) in anhydrous DCM (15 mL) at 0 °C under nitrogen. The reaction mixture was stirred for 15 minutes prior to the dropwise addition of trifluoromethansulfonic anhydride (3.59 g, 12.72 mmol, 2.14 mL). The reaction mixture was slowly allowed to warm to room temperature over 18 hours. The reaction was then quenched and washed with saturated aqueous $NaHCO_3$ solution (2 × 30 mL) and extracted with DCM (30 mL). The combined organic extracts were washed with HCl (1M, 30 mL) and brine (10 mL), dried with $MgSO_4$ and reduced *in vacuo*. The residue was purified *via* flash column chromatography (2% diethyl ether:petrol) to yield *bromotriflate* (2.85 g, 99%) as a colourless oil. ν_{max} (film)/cm^{-1} 3074, 1624, 1576, 1468, 1429, 1248, 1214, 1176, 1137, 1043, 945, 88.6, 780, 764, 741, 705, 655, 621, 595; δ_H (300 MHz, $CDCl_3$) 7.27 (1H, ddd, *J* 7.9, 7.2 and 1.9, Ar-*H*), 7.35 (1H, dd, *J* 8.3 and 2.3, Ar-*H*), 7.41 (1H, ddd, *J* 8.3, 7.2 and 1.9, Ar-*H*), 7.70 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 116.4, 119.0 (q, J_{CF} 320.1), 123.3, 129.5, 129.9, 134.9, 147.5; *m/z* HRMS (EI$^+$) calc. for $C_7H_4BrF_3SO_3$: 303.9011 $[M]^+$; found: 303.9006 $[M]^+$.

Preparation of **(2-iodophenoxy)-trimethylsilane**



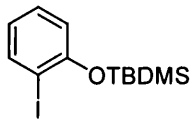
Triethylamine (0.23 g, 2.27 mmol, 0.32 mL) was added to a solution of 2-iodophenol (0.50 g, 2.27 mmol) in anhydrous THF (2.50 mL) at room temperature, under nitrogen, prior to the dropwise addition of trimethylsilyl chloride (0.30 g, 2.73 mmol, 0.35 mL). The reaction mixture was stirred overnight until completion. The reaction mixture was filtered through a plug of celite, washed with hexanes, reduced *in vacuo* and purified *via* flash column chromatography (petrol) to yield *protected phenol* (416 mg, 63%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 0.33 (9H, s, $Si(CH_3)_3$), 6.70 (1H, td, *J* 7.5 and 1.5, Ar-*H*), 6.83 (1H, dd, *J* 8.3 and 1.5, Ar-*H*), 7.21 (1H, td, *J* 7.2 and 1.5, Ar-*H*), 7.75 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.5, 91.1, 119.1, 123.1, 129.3, 139.3, 155.2. Data are in agreement with literature values.[22,23]

Preparation of **(2-iodophenoxy)-triethylsilane**



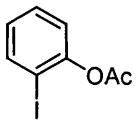
Triethylamine (0.23 g, 2.27 mmol, 0.32 mL) was added to a solution of 2-iodophenol (0.50 g, 2.27 mmol) in anhydrous THF (2.50 mL) at room temperature, under nitrogen, prior to the dropwise addition of triethylsilyl chloride (0.41 g, 2.73 mmol, 0.46 mL). The reaction was complete after stirring at room temperature for 40 minutes. The reaction mixture was filtered through a plug of celite, washed with hexanes, reduced *in vacuo* and purified *via* flash column chromatography (petrol) to yield *protected phenol* (0.74 g, 97%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3061, 2956, 2911, 2879, 1581, 1471, 1436, 1412, 1380, 1288, 1245, 1157, 1116, 1043, 1020, 975, 912, 749, 675, 638; δ_H (300 MHz, $CDCl_3$) 0.82 (6H, qd, *J* 7.9 and 1.5, Si(CH_2CH_3)$_3$), 1.03 (9H, app. t, *J* 7.9, Si(CH_2CH_3)$_3$), 6.69 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 6.83 (1H, dd, *J* 7.9 and 1.5, Ar-*H*), 7.20 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 7.75 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 5.7, 7.2, 91.3, 119.0, 123.2, 129.7, 139.8, 155.7; *m/z* LRMS (EI$^+$) 305 [M-C_2H_5]$^+$, 277 [M-C_4H_{10}]$^+$; (CI$^+$, NH_3) 352 [M+NH_4]$^+$, 322 [M-C_2H_6+NH_4]$^+$; HRMS (EI$^+$) calc. for $C_7H_5BrF_3SO_3$: 334.0244 [M+H]$^+$; found: 334.0242 [M+H]$^+$.

Preparation of **(2-iodophenoxy)-*tert*-butyldimethylsilane**



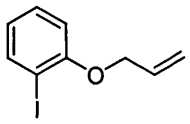
Triethylamine (0.23 g, 2.27 mmol, 0.32 mL) was added to a solution of 2-iodophenol (0.50 g, 2.27 mmol) in anhydrous THF (2.50 mL) at room temperature, under nitrogen, prior to the dropwise addition of *tert*-butyldimethylsilyl chloride (0.41 g, 2.73 mmol, 0.46 mL). The reaction was complete after stirring at room temperature for 1.5 hours. The reaction mixture was filtered through a plug of celite, washed with hexanes, reduced *in vacuo* and purified *via* flash column chromatography (petrol) to yield *protected phenol* (525 mg, 68%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 0.30 (6H, s, Si(CH_3)$_2$), 1.09 (9H, s, SiC(CH_3)$_3$), 6.69 (1H, td, *J* 7.5 and 1.5, Ar-*H*), 6.84 (1H, dd, *J* 7.9 and 1.5, Ar-*H*), 7.21 (1H, td, *J* 7.5 and 1.5, Ar-*H*), 7.77 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) –3.5, 18.8, 26.3, 91.0, 119.0, 123.2, 129.7, 140.0, 155.6. Data are in agreement with literature values.[24-26]

Preparation of **1-acetoxy-2-iodobenzene or Acetic acid 2-iodophenylester**



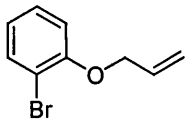
Acetic anhydride (0.35 g, 3.41 mmol, 0.32 mL) was added to a solution of 2-iodophenol (0.50 g, 2.27 mmol) in anhydrous DCM (2.50 mL) at room temperature, under nitrogen, prior to the addition of trimethylsilyltrifluoromethane sulfonate (0.01 g, 0.05 mmol, 0.01 mL). The reaction was complete after stirring at room temperature for 35 minutes. The reaction mixture was quenched with MeOH (2.50 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL) and water (2 × 10 mL), dried over $MgSO_4$ and reduced *in vacuo*. The resulting crude oil was purified *via* flash column chromatography (petrol) to yield *protected phenol* (0.56 g, 94%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 2.37 (3H, s, OCOC*H*$_3$), 6.98 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 7.10 (1H, dd, *J* 7.9 and 1.5, Ar-*H*), 7.37 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 7.83 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 21.3, 90.5, 122.9, 127.6, 129.4, 139.4, 151.1, 168.7. Data are in agreement with literature values.[27,28]

Preparation of **1-allyloxy-2-iodobenzene**



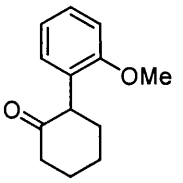
Potassium carbonate (0.63 g, 4.55 mmol) was added to a solution of 2-iodophenol (1.00 g, 4.55 mmol) in anhydrous THF (5.00 mL) at room temperature, under nitrogen. Upon heating the reaction mixture to 40°C, allyl bromide (0.66 g, 5.45 mmol, 0.47 mL) was added and the reaction mixture stirred over 18 hours. The reaction mixture was then cooled, filtered through a plug of celite, washed with hexane, reduced *in vacuo* and purified *via* flash column chromatography (petrol) to yield *protected phenol* (1.11 g, 94%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 4.60 (2H, dt, *J* 4.9 and 1.7, OC*H*$_2$), 5.32 (1H, app. dt, *J* 10.7 and 1.5, (*cis*)-C=C*H*), 5.53 (1H, app. dq, *J* 17.3 and 1.7, (*trans*)-C=C*H*), 6.00-6.13 (1H, m, CH_2CH=CH_2), 6.72 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 6.81 (1H, dd, *J* 7.9 and 1.5, Ar-*H*), 7.28 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 7.78 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 69.6, 86.7, 112.5, 117.7, 122.6, 129.4, 132.6, 139.5, 157.1. Data are in agreement with literature values.[29-31]

Preparation of **1-allyloxy-2-bromobenzene**



As for 1-allyloxy-2-iodobenzene, employing 2-bromophenol (1.57 g, 9.07 mmol, 1.05 mL) to yield *protected phenol* (1.51 g, 78%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 4.62 (2H, dt, *J* 4.9 and 1.5, OCH_2), 5.32 (1H, dq, *J* 10.6 and 1.5, (*cis*)-C=C*H*), 5.49 (1H, dq, *J* 16.9 and 1.9, (*trans*)-C=C*H*), 6.00-6.14 (1H, m, $CH_2CH=CH_2$), 6.84 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 6.89 (1H, dd, *J* 8.3 and 1.5, Ar-*H*), 7.25 (1H, td, *J* 7.9 and 1.5, Ar-*H*), 7.55 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 70.0, 112.7, 114.0, 118.2, 122.4, 128.8, 133.0, 133.8, 155.3. Data are in agreement with literature values.[29]

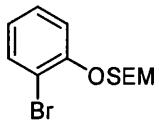
Preparation of **2-(2-methoxyphenyl)-cyclohexanone**



Sodium *tert*-butoxide (77 mg, 0.80 mmol) was added to a flask charged with $Pd(OAc)_2$ (3 mg, 0.01 mmol) and 1-dicyclohexylphosphino-1'-methylbiphenyl (12 mg, 0.03 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.54 mL). *O*-Bromoanisole (100 mg, 0.05 mmol, 0.07 mL) and cyclohexanone (63 mg, 0.64 mmol, 0.07 mL) were added and the reaction heated to 80 °C for 24 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (5 to 10% diethyl ether:petrol) and recrystallised from diethyl ether to yield *ketone* (58 mg, 54%) as colourless crystals: mp 69-71°C. ν_{max} (KBr)/cm^{-1} 3410, 3065, 3034, 3000, 2937, 2861, 2837, 1715, 1602, 1602, 1588, 1495, 1463, 1357, 1338, 1322, 1291, 1245, 1200, 1174, 1125, 1065, 1052, 1029, 976, 929, 825, 753; δ_H (300 MHz, $CDCl_3$) 1.71-1.91 (2H, m, CH_2), 1.93-2.12 (2H, m, CH_2), 2.13-2.28 (2H, m, $ArCHCH_2$), 2.42-2.59 (2H, m, CH_2CO), 3.78 (3H, s, OCH_3), 3.95 (1H, app. dd, *J* 12.6 and 5.4, Ar-C*H*), 6.89 (1H, d, *J* 7.5, Ar-*H*), 6.96 (1H, td, *J* 7.5 and 1.1, Ar-*H*), 7.13 (1H, dd, *J* 7.5 and 1.9, Ar-*H*), 7.25 (1H, td, *J* 7.5 and 1.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 26.1, 27.9, 33.8, 41.8, 51.4, 55.8, 111.0, 120.9, 128.3, 128.4, 129.1, 157.3, 210.3; *m/z* LRMS (EI^+) 205 $[M+H]^+$ (14%), 204 $[M]^+$ (83%), 160 $[M-CO_2]^+$ (47%); (CI^+, NH_3) 222

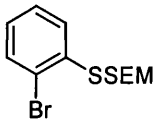
$[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{13}H_{17}O_2$: 205.1223 $[M+H]^+$; found: 205.1221 $[M+H]^+$.

Preparation of **[2-(2-bromophenoxymethoxy)-ethyl]-trimethylsilane, 205**



A solution of 2-bromophenol (2.00 g, 11.56 mmol, 1.34 mL) in anhydrous DMF (10 mL) was added dropwise to a solution of sodium hydride (60 % dispersion in mineral oil, 0.49 g, 20.35 mmol) in anhydrous DMF (10 mL) at 0 °C under nitrogen. The reaction mixture was allowed to stir for 30 minutes prior to the dropwise addition of trimethylsilylethoxymethyl chloride (2.31 g, 13.87 mmol, 2.46 mL) over 15 minutes at 0°C. The reaction mixture was allowed to stir for a further 2 hours at room temperature. The reaction mixture was then quenched with water (60 mL), extracted with diethyl ether (2 × 30 mL) and the combined organic extracts washed with brine (50 mL), dried over $MgSO_4$, filtered and reduced *in vacuo.* The mixture was purified *via* filtration through a plug of silica (petrol) to yield *protected phenol* **205** (3.10 g, 94%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3551, 3356, 3068, 2953, 1683, 1596, 1506, 1448, 1416, 1331, 1246, 1210, 1143, 1104, 1027, 983, 887, 756, 695, 648, 607; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.93-1.00 (2H, m, CH_2Si), 3.85-3.78 (2H, m, OCH_2CH_2), 5.30 (2H, app. s, OCH_2O), 6.88 (1H, ddd, *J* 7.9, 7.2 and 1.9, Ar-*H*), 7.17 (1H, dd, *J* 8.3 and 1.9, Ar-*H*), 7.25 (1H, ddd, *J* 8.3, 7.2 and 1.5, Ar-*H*), 7.54 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 18.0, 66.6, 93.5, 112.8, 116.2, 122.9, 128.4, 133.3, 153.9; *m/z* LRMS (CI^+, NH_3) 320 $[M+NH_4:^{79}Br]^+$, 322 $[M+NH_4:^{81}Br]^+$; HRMS (ES^+) calc. for $C_{12}H_{23}BrNO_2Si$: 320.0676 $[M+NH_4]^+$; found: 320.0677 $[M+NH_4]^+$.

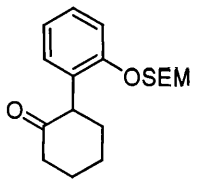
Preparation of **[2-(2-bromophenylsulfanylmethoxy)-ethyl]-trimethylsilane, 216**



A solution of 2-bromobenzenethiol (2.00 g, 10.58 mmol, 1.27 mL) in anhydrous DMF (10 mL) was added dropwise to a solution of triethylamine (1.18 g, 11.64 mmol, 1.62 mL) in anhydrous DMF (10 mL) at 0 °C under nitrogen. The reaction mixture was

allowed to stir for 30 minutes prior to the dropwise addition of trimethylsilylethoxymethyl chloride (2.12 g, 12.69 mmol, 2.25 mL) over 15 minutes at 0°C. The reaction mixture was allowed to stir for a further 2 hours at room temperature. The reaction mixture was then quenched with water (60 mL), extracted with diethyl ether (2 × 30 mL) and the combined organic extracts washed with brine (50 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The mixture was purified *via* filtration through a plug of silica (petrol) to yield *protected phenol* **216** (2.95 g, 87%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3061, 2953, 2947, 2825, 1584, 1482, 1440, 1382, 1303, 1249, 1199, 1180, 1071, 1026, 967, 940, 898, 860, 836, 740, 704, 692; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, Si(CH_3)$_3$), 0.88-0.96 (2H, m, CH_2Si), 3.62-3.70 (2H, m, OCH_2CH_2), 4.97 (2H, app. s, OCH_2S), 7.15-7.21 (1H, m, Ar-*H*), 7.22-7.29 (1H, m, Ar-*H*), 7.42-7.47 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.1, 67.3, 76.9, 127.9, 130.3, 131.4, 137.8; *m/z* LRMS (CI$^+$, NH_3) 336 [M+NH_4:^{79}Br]$^+$, 338 [M+NH_4:^{81}Br]$^+$; HRMS (ES$^+$) calc. for $C_{12}H_{23}BrNOSSi$: 336.0448 [M+NH_4:^{79}Br]$^+$; found: 336.0449 [M+NH_4:^{79}Br]$^+$.

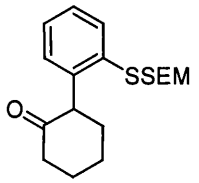
Preparation of **2-[2-(2-trimethylsilanylethoxymethoxy)-phenyl]-cyclohexanone, 206**



Sodium *tert*-butoxide (328 mg, 3.42 mmol) was added to a flask charged with $Pd_2(dba)_3$ (52 mg, 0.06 mmol) and $HP^tBu_3BF_4$ (40 mg, 0.14 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (2.30 mL). [2-(2-Bromo-phenoxymethoxy)-ethyl]-trimethylsilane **205** (700 mg, 2.28 mmol) and cyclohexanone (268 mg, 2.73 mmol, 0.28 mL) were added and the reaction heated to 100 °C for 20 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (5 to 10 % diethyl ether:petrol) to yield *ketone* **206** (626 mg, 85 %) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3065, 3040, 2951, 2897, 2863, 1716, 1603, 1588, 1494, 1451, 1412, 1380, 1356, 1321, 1300, 1249, 1228, 1200, 1150, 1121, 1089, 1050, 1002, 936, 920, 860, 836, 753, 694; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, Si(CH_3)$_3$), 0.92-0.99 (2H, m, CH_2Si) 1.71-1.92 (2H, m, *cyc*-CH_2), 1.95-2.09 (2H, m, *cyc*-CH_2), 2.10-2.30 (2H, m, ArCHCH_2), 2.41-2.59 (2H, m, *cyc*-CH_2CO), 3.64-3.78 (2H, m, OCH_2CH_2),

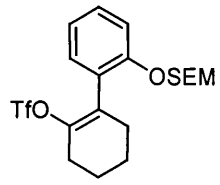
3.95 (1H, app. dd, *J* 12.6 and 5.4, Ar-C*H*), 5.18 (2H, AB q, ν_A 5.14 and ν_B 5.18, *J* 6.6, OCH_2O), 6.99 (1H, td, *J* 7.5 and 1.1, Ar-*H*), 7.10-7.15 (2H, m, Ar-*H*), 7.22 (1H, ddd, *J* 8.3, 7.2 and 1.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.4, 27.1, 28.9, 34.8, 43.7, 52.6, 67.6, 94.5, 115.5, 123.0, 129.4, 129.8, 130.2, 156.4, 211.0; *m/z* LRMS (CI^+, NH_3) 338 $[M+NH_4]^+$, 173 $[C_{12}OH_{13}]$; HRMS (ES^+) calc. for $C_{18}H_{32}NO_3Si$: 338.2146 $[M+NH_4]^+$; found: 338.2151 $[M+NH_4]^+$.

Preparation of **2-[2-(2-trimethylsilanylethoxymethylsulfanyl)-phenyl]-cyclohexanone, 217**



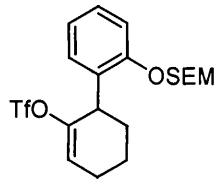
Sodium *tert*-butoxide (450 mg, 4.69 mmol) was added to a flask charged with $Pd_2(dba)_3$ (72 mg, 0.08 mmol) and $HP^tBu_3BF_4$ (55 mg, 0.19 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (3.00 mL). [2-(2-Bromo-phenylsulfanylmethoxy)-ethyl]-trimethylsilane **216** (1.00 g, 3.13 mmol) and cyclohexanone (369 mg, 3.76 mmol, 0.39 mL) were added and the reaction heated to 100 °C for 20 hours. After cooling, the reaction mixture was diluted with diethyl ether (ca. 10 mL), filtered through celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (5 to 10% diethyl ether:petrol) to yield *ketone* **217** (478 mg, 45%) as an amber oil. ν_{max} (NaCl)/cm^{-1} 3059, 3024, 2949, 2895, 2882, 1713, 1651, 1590, 1472, 1448, 1381, 1352, 1305, 1249, 1202, 1180, 1125, 1074, 971, 939, 898, 860, 836, 757, 698, 669; δ_H (300 MHz, $CDCl_3$) 0.0 (9H, s, Si(CH_3)$_3$), 0.91-0.98 (2H, m, CH_2Si), 1.74-1.93 (2H, m, *cyc*-CH_2), 1.94-2.12 (2H, m, *cyc*-CH_2), 2.13-2.32 (2H, m, ArCHCH_2), 2.50-2.57 (2H, m, *cyc*-CH_2CO), 3.58-3.73 (2H, m, OCH_2CH$_2$) 4.29 (1H, app. dd, *J* 12.6 and 5.4, Ar-C*H*), 4.88 (2H, AB q, ν_A 4.83 and ν_B 4.89, *J* 11.3, OCH_2S), 7.13-7.29 (3H, m, Ar-*H*), 7.62-7.67 (1H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.2, 27.2, 29.0, 36.0, 43.8, 56.2, 67.9, 128.4, 128.7, 128.9, 129.8, 133.6, 137.0, 141.6, 211.2; *m/z* LRMS (CI^+, NH_3) 354 $[M+NH_4]^+$, 337 $[M+H]^+$, 307 $[M-CH_2O]^+$, 278 $[M-C_3H_6O]^+$, 189 $[M-C_6SiO_2H_{15}]^+$; HRMS (ES^+) calc. for $C_{18}H_{32}NO_2SSi$: 354.1918 $[M+NH_4]^+$; found: 354.1918 $[M+NH_4]^+$.

Preparation of **2-[2-(2-trimethylsilanylethoxymethoxy)-phenyl]-cyclohexen-1-yl trifluoromethanesulfonate, 210**



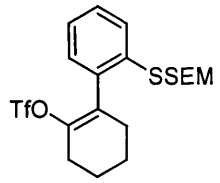
KHMDS (0.5M in toluene, 5.15 mmol, 10.30 mL) was added dropwise to a solution of *ketone* **206** (1.50 g, 4.68 mmol) in anhydrous THF (4.70 mL) at 0 °C under nitrogen. The solution turned bright yellow in colour. The reaction mixture was stirred for 2 hours at 0 °C prior to the addition of 2-[*N,N-bis*(trifluoromethanesulfonyl) amino]-5-chloropyridine **172** (2.02 g, 5.148 mmol) in one portion, turning the solution orange in colour. The reaction mixture was allowed to slowly warm to room temperature over 18 hours. The mixture was quenched with a saturated aqueous Na_2CO_3 solution (30 mL), extracted with diethyl ether (2 × 30 mL) and the organic extracts combined, dried over $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (2% diethyl ether:petrol) to yield *triflate* **210** (1.58 g, 76%) as a pale amber oil. ν_{max} (NaCl)/cm^{-1} 3062, 3028, 2952, 2866, 1603, 1582, 1494, 1449, 1416, 1381, 1309, 1247, 1209, 1144, 1117, 1089, 1031, 1000, 892, 855, 837, 815, 754, 731, 695, 616; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, Si(CH_3)$_3$), 0.92-1.00 (2H, m, CH_2Si), 1.70-1.82 (2H, m, *cyc*-CH_2), 1.83-1.95 (2H, m, *cyc*-CH_2), 2.41-2.53 (4H, m, ArCCH_2 and CH_2C=C), 3.74 (2H, app. t, *J* 8.3, OCH_2CH$_2$), 5.21 (2H, app. s, OCH_2O), 6.98 (1H, td, *J* 7.2 and 1.1, Ar-*H*), 7.10 (1H, dd, *J* 7.9 and 1.9, Ar-*H*) 7.15 (1H, dd, *J* 7.9 and 1.1, Ar-*H*), 7.26 (1H, td, *J* 7.2 and 1.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.5, 23.4, 24.6, 29.3, 31.9, 67.7, 94.5, 115.9, 119.6 (d, J_{CF} 319.8), 122.8, 127.9, 130.4, 130.8, 131.3, 145.5, 155.8; *m/z* LRMS (CI$^+$, NH_3) 470 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{19}H_{31}F_3NO_5SSi$: 470.1639 [M+NH_4]$^+$; found: 470.1642 [M+NH_4]$^+$.

Preparation of **6-[2-(2-trimethylsilanylethoxymethoxy)-phenyl]-cyclohexen-1-yl trifluoromethanesulfonate, 212**



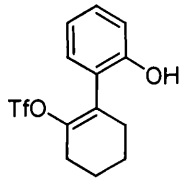
KHMDS (0.5M in toluene, 1.72 mmol, 3.43 mL) was added dropwise to a solution of *ketone* **210** (500 mg, 1.56 mmol) in anhydrous THF (1.50 mL) at -78 °C under nitrogen. The solution turned bright yellow in colour. The reaction mixture was stirred for 30 minutes at -78 °C prior to the addition of 2-[*N,N-bis*(trifluoromethanesulfonyl) amino]-5-chloropyridine **172** (674 mg, 1.72 mmol) in one portion, turning the solution orange in colour. The reaction mixture was allowed to slowly warm to room temperature overnight. The mixture was quenched with a saturated aqueous Na_2CO_3 solution (30 mL), extracted with diethyl ether (2 × 30 mL) and the organic extracts combined, dried over $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (0-2% diethyl ether:petrol) to yield *triflate* **212** (470 mg, 67%) as a pale amber oil. ν_{max} (NaCl)/cm^{-1} 3066, 2953, 1683, 1601, 1588, 1491, 1448, 1417, 1246, 1210, 1144, 1111, 1088, 1028, 1000, 909, 858, 838, 755, 606; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 1.52-1.63 (2H, m, CH_2Si), 1.75-1.87 (2H, m, *cyc*-CH_2), 2.02-2.15 (2H, m, *cyc*-CH_2), 2.25-2.34 (2H, m, *cyc*-CH_2), 4.16-4.23 (1H, m, Ar-C*H*), 5.26-6.04 (2H, m, OCH_2CH_2), 5.26 (2H, app. s, OCH_2O), 6.04 (1H, td, *J* 4.4 and 1.1, C=C*H*), 6.93-6.99 (1H, m, Ar-*H*), 7.11-7.17 (2H, m, Ar-*H*), 7.18-7.25 (1H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 18.0, 18.3, 24.4, 30.8, 37.8, 66.3, 92.7, 113.9, 119.9 (q, J_{CF} 320.1), 120.9, 121.2, 129.1, 128.6, 128.7, 149.7, 154.9; *m/z* LRMS (EI^+) 452 $[M]^+$ (40%), 409 $[M-C_3H_7]^+$ (68%), 407 $[M-C_3H_9]^+$ (100%); (CI^+, NH_3) 470 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{19}H_{31}F_3NO_5SSi$: 470.1639 $[M+NH_4]^+$; found: 170.1644 $[M+NH_4]^+$.

Preparation of **2-[2-(2-trimethylsilanylethoxymethylsulfanyl)-phenyl]-cyclohexen-1-yl trifluoromethanesulfonate, 218**



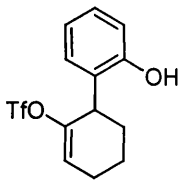
KHMDS (0.5M in toluene, 1.63 mmol, 3.30 mL) was added dropwise to a solution of *ketone* **217** (500 mg, 1.49 mmol) in anhydrous THF (1.50 mL) at 0 °C under nitrogen. The solution turned bright amber in colour. The reaction mixture was stirred for 2 hours at 0 °C prior to the addition of 2-[*N,N-bis*(trifluoromethanesulfonyl) amino]-5-chloropyridine **172** (642 mg, 1.63 mmol) in one portion, turning the solution orange in colour. The reaction mixture was allowed to slowly warm to room temperature over 18 hours. The mixture was quenched with a saturated aqueous Na_2CO_3 solution (30 mL), extracted with diethyl ether (2 × 30 mL) and the organic extracts combined, dried over $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (2% diethyl ether:petrol) to yield *triflate* **218** (620 mg, 89%) as an amber oil. ν_{max} (NaCl)/cm^{-1} 3060, 2952, 2895, 2870, 1588, 1447, 1416, 1343, 1307, 1247, 1209, 1142, 1076, 1031, 993, 964, 930, 891, 851, 810, 755, 693, 618, 604; δ_H (300 MHz, $CDCl_3$) 0.0 (9H, s, Si(C*H*$_3$)$_3$), 0.96 (2H, app. dd, *J* 9.3 and 7.4, C*H*$_2$Si), 1.71-1.82 (2H, m, *cyc*-C*H*$_2$), 1.85-1.96 (2H, m, *cyc*-C*H*$_2$), 2.21-2.37 (1H, m, ArCC*H*$_2$), 2.42-2.57 (3H, m, ArCC*H*$_2$ and C=CC*H*$_2$), 3.68 (2H, app. dd, *J* 9.3 and 7.4, OC*H*$_2$CH$_2$), 4.99 (2H, AB q, ν_A 4.95 and ν_B 5.01, *J* 11.7, OC*H*$_2$O), 7.10 (1H, dd, *J* 7.5 and 1.5, Ar-*H*), 7.21 (1H, td, *J* 7.5 and 1.1, Ar-*H*) 7.28 (1H, td, *J* 7.5 and 1.5, Ar-*H*), 7.64 (1H, dd, *J* 7.5 and 1.1, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.1, 23.3, 24.4, 29.1, 32.4, 67.5, 76.2, 119.5 (d, J_{CF} 326.8), 127.6, 130.7, 136.7, 132.2, 138.5, 140.5, 145.9, 150.8; *m/z* LRMS (CI$^+$, NH_3) 486 $[M+NH_4]^+$; HRMS (ES$^+$) calc. for $C_{19}H_{31}F_3NO_4S_2Si$: 486.1410 $[M+NH_4]^+$; found: 486.1411 $[M+NH_4]^+$.

Preparation of **2-[2-hydroxyphenyl]-cyclohexen-1-yl trifluoromethanesulfonate, 213**



HCl (1M in H_2O, 5.10 mmol, 5.10 mL) was added to a solution of *triflate* **210** (1.50 g, 3.40 mmol) in THF (3.40 mL) and the reaction mixture heated to 80 °C for 4 hours. The reaction was quenched with a saturated aqueous Na_2CO_3 solution (30 mL), extracted with diethyl ether (2 × 30 mL) and the organic extracts combined, dried over $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *phenol* **213** (0.90 g, 82%) as pale amber oil. ν_{max} (NaCl)/cm^{-1} 3544 (br), 3067, 3038, 2945, 2866, 1694, 1609, 1586, 1504, 1489, 1449, 1411, 1342, 1291, 1245, 1209, 1139, 1103, 1078, 1028, 994, 962, 893, 856, 830, 797, 755, 679, 660, 617, 604; δ_H (300 MHz, $CDCl_3$) 1.74-1.85 (2H, m, C*H*$_2$), 1.86-1.96 (2H, m, C*H*$_2$), 2.39-2.53 (4H, m, ArCC*H*$_2$ and C*H*$_2$C=C), 4.88 (1H, s (br), Ar-O*H*), 6.90 (1H, dd, *J* 8.1 and 0.9, Ar-*H*), 6.95 (1H, td, *J* 7.5 and 1.1, Ar-*H*), 7.07 (1H, dd, *J* 7.7 and 1.7, Ar-*H*), 7.23 (1H, ddd, *J* 9.0, 7.2 and 1.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 21.9, 23.0, 27.9, 30.6, 117.9 (d, J_{CF} 320), 116.3, 120.9, 123.7, 127.9, 129.3, 129.7, 145.4, 152.0; *m/z* LRMS (EI$^+$) 189 $[M\text{-}CF_3SO_2]^+$ (22%), 172 $[M\text{-}CF_3HSO_3]^+$ (21%), 169 $[M\text{-}C_2F_3SO_3]^+$ (24%), 107 $[C_7H_7O]^+$; (CI$^+$) 340 $[M+NH_4]^+$; HRMS (ES$^+$) calc. for $C_{13}H_{17}F_3NO_4S$: 340.0825 $[M+NH_4]^+$; found: 340.0825 $[M+NH_4]^+$.

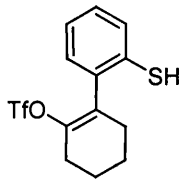
Preparation of **6-[2-hydroxyphenyl]-cyclohexen-1-yl trifluoromethanesulfonate, 214**



HCl (2M in H_2O, 0.66 mmol, 0.33 mL) was added to a solution of *triflate* **212** (200 mg, 0.44 mmol) in THF (0.40 mL) and the reaction mixture heated to 80 °C for 6 hours. The reaction was quenched with a saturated aqueous Na_2CO_3 solution (30 mL), extracted with diethyl ether (2 × 30 mL) and the organic extracts combined, dried with $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *phenol* **214** (117 mg, 82%) as pale amber oil. ν_{max} (NaCl)/cm^{-1} 3551 (br), 3070, 3039, 2939, 2865, 1684, 1608, 1594, 1505,

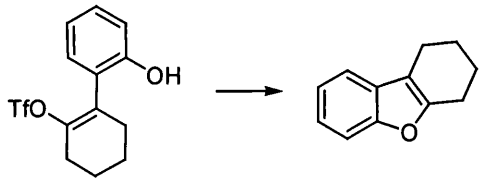
1456, 1413, 1330, 1245, 1211, 1141, 1096, 1025, 982, 902, 888, 856, 825, 755, 610; δ_H (300 MHz, $CDCl_3$) 1.55-1.66 (2H, m, C*H*$_2$), 1.82-1.93 (1H, m, ArCC*H*$_2$), 2.04-2.19 (1H, m, ArCC*H*$_2$), 2.36-2.27 (2H, m, C*H*$_2$C=C), 4.11-4.18 (1H, m, Ar-C*H*), 4.78 (1H, s, Ar-O*H*), 6.05 (1H, td, *J* 4.1 and 1.1, C=C*H*), 6.75 (1H, dd, *J* 7.9 and 1.3, Ar-*H*), 6.92 (1H, td, *J* 7.9 and 1.3, Ar-*H*), 7.10-7.17 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 18.4, 24.3, 30.5, 38.0, 115.6, 118.7 (d, J_{CF} 358.2), 120.9, 121.1, 126.5, 128.1, 129.1, 149.5, 153.1; *m/z* LRMS (EI^+) 322 $[M]^+$ (100%), 172 $[M\text{-}CF_3HSO_3]^+$ (80%); (CI^+, NH_3) 340 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{13}H_{17}F_3NO_4S$: 340.0825 $[M+NH_4]^+$; found: 340.0826 $[M+NH_4]^+$.

Preparation of **2-[2-thiolphenyl]-cyclohexen-1-yl trifluoromethanesulfonate, 219**



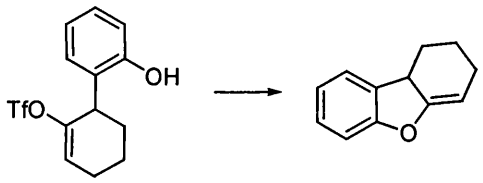
Silver nitrate (1.09 g, 6.40 mmol) and 2,6-lutidine (0.37 g, 3.41 mmol, 0.40 mL) were added to a solution of *triflate* **218** (0.20 g, 0.43 mmol) in THF-H_2O (4.80: 1.20 mL). The reaction mixture was stirred at room temperature for one hour until complete. The mixture was then acidified with acetic acid (2 mL), diluted with diethyl ether (*ca.* 10 mL) and filtered through a plug of celite. The ether fraction was washed with a saturated aqueous $CuSO_4$ solution (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$ and reduced *in vacuo*. The residue was purified *via* flash column chromatography (3% diethyl ether: petrol) to yield *benzenethiol* **219** (74 mg, 68%) as an amber oil. ν_{max} (NaCl)/cm^{-1} 3446 (br), 2937, 2864, 1684, 1652, 1587, 1447, 1416, 1245, 1210, 1141, 1080, 1032, 992, 890, 850, 808, 754, 617, 602; δ_H (300 MHz, $CDCl_3$) 1.58 (1H, s (br), Ar-S*H*), 1.72-1.85 (2H, m, C*H*$_2$), 1.86-1.97 (2H, m, C*H*$_2$), 2.24-2.53 (4H, m, ArCC*H*$_2$ and C*H*$_2$C=C), 7.08-7.14 (1H, m, Ar-*H*), 7.19-7.30 (2H, m, Ar-*H*), 7.53-7.60 (1H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 21.9, 22.9, 27.8, 31.0, 121.0 (q, J_{CF} 320.0) 126.8, 127.1, 128.9, 129.4, 134.6, 135.5, 135.8, 145.4; *m/z* LRMS (EI^+) 337 $[M\text{-}H]^+$; (CI^+, NH_3) 356 $[M+NH_4]^+$, 222 $[M\text{-}SO_2CF_3+NH_3]^+$, 188 $[M\text{-}HS_2O_2CF_3+NH_3]^+$; HRMS (EI) calc. for $C_{13}H_{12}F_3O_3S_2$: 337.0174 $[M\text{-}H]^+$; found: 337.0175 $[M\text{-}H]^+$.

Preparation of **1,2,3,4-tetrahydro-dibenzofuran, 89**



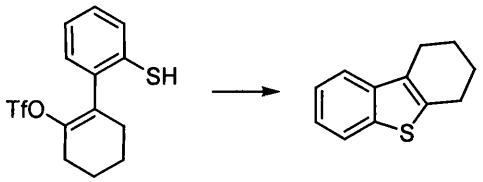
Cesium carbonate (76 mg, 0.233 mmol) was added to a flask charged with $Pd_2(dba)_3$ (4 mg, 0.01 mmol) and DPEphos (5 mg, 0.01 mmol) under nitrogen and the reagents suspended in anhydrous dioxane (0.30 mL). *Phenol* **213** (50 mg, 0.16 mmol) was added and the reaction heated to 100 °C for 20 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (petrol) to yield *benzofuran* **89** (25 mg, 95%) as a colourless oil. Data collected were in agreement with previous experimental analysis for *benzofuran* **89** (*pg.* 142).

Preparation of **1,2,3,9b-tetrahydro-dibenzofuran, 215**



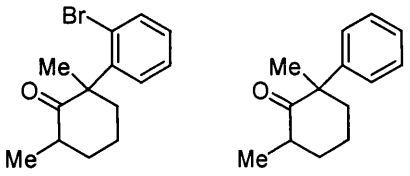
Following the procedure as for **89**, using *phenol* **214** (50 mg, 0.155 mmol) yielded the *benzofuran* **215**. The crude NMR showed peaks corresponding to the desired product: δ_H (300 MHz, $CDCl_3$) 3.53-3.64 (1H, m, Ar-C*H*), 5.23 (1H, dd, *J* 6.9 and 3.6, C=C*H*). Due to isomerisation of the double bond, benzofuran **89** was isolated (24 mg, 91%) as a colourless oil. Data collected were in agreement with previous experimental analysis for *benzofuran* **89** (*pg.* 142).

Preparation of **1,2,3,4-tetrahydro-dibenzothiophene, 155**



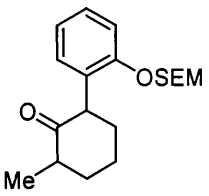
Following the procedure as for **89**, using *thiol* **219** (50 mg, 0.15 mmol) yielded *benzothiophene* **155** (13 mg, 47%) as a colourless oil. Data collected were in agreement with previous experimental analysis for *benzothiophene* **155** (*pg.* 152-153).

Preparation of **2-(2-Bromo-phenyl)-2,6-dimethyl-cyclohexanone, A**; **2,6-Dimethyl-2-phenyl cyclohexanone, B**



Sodium *tert*-butoxide (1.02 g, 10.60 mmol) was added to a flask charged with $Pd_2(dba)_3$ (162 mg, 0.18 mmol) and $HP^tBu_3BF_4$ (123 mg, 0.42 mmol) under nitrogen and the reagents suspended in anhydrous toluene (7.00 mL). 1-Bromo-2-iodobenzene (2.00 g, 7.07 mmol, 0.91 mL) and 2,6-dimethylcyclohexanone (1.07 g, 8.48 mmol, 1.16 mL) were added and the reaction heated to 100 °C for 14 hours. After cooling, the reaction mixture was diluted with diethyl ether (*ca.* 30 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (2% diethyl ether:petrol) to yield none of the desired *ketone* **A** but *ketone* **B** (399 mg, 28%) as a yellow oil. ν_{max} (NaCl)/cm^{-1} 3087, 3059, 3025, 2967, 2931, 2863, 1706, 1494, 1465, 1448, 1507, 1374, 1314, 1091, 1029, 979, 955, 764, 698; δ_H (300 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.6, CHCH_3), 1.26 (3H, s, ArCCH_3), 1.42 (1H, app. td, *J* 12.9 and 3.8, ArCCH_2), 1.63-1.76 (2H, m, CH_2), 1.79-1.89 (1H, m, CH_2), 1.92-1.99 (1H, m, CH_2), 2.48 (1H, app. sept., *J* 6.3, CH_2), 2.68-2.75 (1H, m, Ar-C*H*), 7.15 (2H, d, *J* 7.5, Ar-*H*), 7.23 (1H, t, *J* 7.5, Ar-*H*), 7.34 (2H, t, *J* 7.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 15.2, 22.4, 29.3, 38.1, 39.0, 42.9, 54.8, 126.5, 126.8, 129.4, 144.3, 215.7; *m/z* LRMS (EI^+) 203 $[M+H]^+$ (15%), 202 $[M]^+$ (100%), 144 $[M-C_3H_7O]^+$ (75%); HRMS (EI^+) calc. for $C_{14}H_{18}O$: 202.1358 $[M]^+$; found: 202.1343 $[M]^+$.

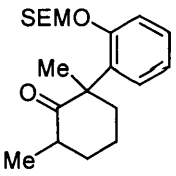
Preparation of **2-methyl-6-[2-(2-trimethylsilanylethoxymethoxy)-phenyl]-cyclohexanone, 221**



Sodium *tert*-butoxide (94 mg, 0.98 mmol) was added to a flask charged with $Pd_2(dba)_3$ (15 mg, 0.02 mmol) and $HP^tBu_3BF_4$ (11 mg, 0.04 mmol) under nitrogen and the reagents suspended in anhydrous toluene (0.70 mL). [2-(2-Bromo-phenoxymethoxy)-ethyl]-trimethylsilane **205** (200 mg, 0.65 mmol) and 2-methylcyclohexanone (80 mg,

0.72 mmol, 0.09 mL) were added and the reaction heated to 100 °C for 16 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *ketone* **221** (180 mg, 83%) as a pale yellow oil. ν_{max} (NaCl)/cm^{-1} 3064, 3039, 2932, 2862, 2798, 1717, 1603, 1589, 1493, 1449, 1411, 1376, 1359, 1249, 1229, 1207, 1185, 1151, 1124, 1091, 1053, 1035, 1002, 937, 916, 862, 834, 791, 751; δ_H (300 MHz, $CDCl_3$) 0.0 (9H, s, Si(CH_3)$_3$), 0.89-0.98 (2H, m, CH_2Si), 1.05 (3H, d, *J* 6.4, CHCH_3), 1.41-1.60 (1H, m, *cyc*-CH_2), 1.81-2.10 (3H, m, *cyc*-CH_2), 2.13-2.29 (2H, m, *cyc*-CH_2), 2.60 (1H, app. sept., *J* 6.4, CH_2), 3.62-3.76 (2H, m, OCH_2CH$_2$), 4.00 (1H, app. dd, *J* 12.2 and 4.8, Ar-C*H*), 5.15 (2H, AB q, ν_A 5.14 and ν_B 5.17, *J* 6.6, OCH_2O), 6.98 (1H, td, *J* 7.5 and 1.1, Ar-*H*), 7.08 (1H, dd, *J* 7.5 and 1.1, Ar-*H*), 7.12 (1H, dd, J 7.5 and 1.5, Ar-*H*), 7.19 (1H, td, *J* 7.5 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 16.3, 19.5, 27.3, 35.6, 38.4, 47.2, 52.2, 67.6, 94.6, 115.4, 122.9, 129.2, 129.8, 130.1, 156.3, 212.1.

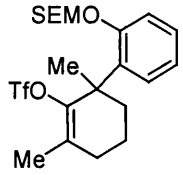
Preparation of **2,6-dimethyl-2-[2-(2-trimethylsilanylethoxymethoxy)-phenyl]-cyclohexanone, 223**



Sodium *tert*-butoxide (78 mg, 0.81 mmol) was added to a flask charged with $Pd_2(dba)_3$ (12 mg, 0.01 mmol) and HP^{t}Bu$_3$BF$_4$ (9 mg, 0.03 mmol) under nitrogen and the reagents suspended in anhydrous toluene (0.60 mL). [2-(2-Bromo-phenoxymethoxy)-ethyl]-trimethylsilane, **205** (200 mg, 0.65 mmol) and 2,6-dimethylcyclohexanone (70 mg, 0.54 mmol, 0.09 mL) were added and the reaction heated to 100 °C for 19 hours. After cooling, the reaction mixture was diluted with diethyl ether (10 mL), filtered through a plug of celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *ketone* **223** (85 mg, 45%) as a pale yellow oil. ν_{max} (NaCl)/cm^{-1} 3062, 2930, 2864, 1717, 1597, 1582, 1489, 1463, 1447, 1462, 1421, 1410, 1370, 1313, 1249, 1227, 1209, 1147, 1125, 1092, 1073, 1056, 1049, 1039, 994, 953, 936, 919, 863, 836, 754; δ_H (300 MHz, $CDCl_3$) 0.0 (9H, s, Si(CH_3)$_3$), 0.89-0.97 (2H, m, CH_2Si), 0.98 (3H, d, *J* 6.4, CHCH_3), 1.23 (3H, s, ArCCH_3), 1.33 (1H, qd, *J* 12.4 and 4.3, *cyc*-CH_2), 1.51-1.64 (2H, m, *cyc*-CH_2), 1.70-1.85 (1H, m, *cyc*-CH_2),

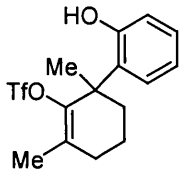
1.85-1.96 (1H, m, *cyc*-CH_2), 2.49-2.60 (1H, m, *cyc*-CH_2), 2.61-2.70 (1H, m, CH_3CHCO), 3.64-3.72 (2H, m, OCH_2CH_2), 5.07 (2H, AB q, ν_A 5.04 and ν_B 5.12 , *J* 7.2, OCH_2O), 7.05 (1H, td, *J* 6.8 and 2.3, Ar-*H*), 7.16-7.25 (2H, m, Ar-*H*), 7.38 (1H, d, *J* 6.8, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 16.5, 19.5, 23.1, 26.9, 40.3, 41.9, 43.2, 54.2, 67.7, 94.5, 116.3, 123.4, 128.1, 129.3, 134.7, 156.6, 217.0.

Preparation of **2,6-dimethyl-2-[2-(2-trimethylsilanylethoxymethoxy)-phenyl]-cyclohexen-1-yl trifluoromethanesulfonate, 225**



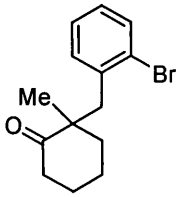
KHMDS (0.5M in toluene, 0.95 mmol, 1.89 mL) was added dropwise to a solution of *ketone* **223** (300 mg, 0.86 mmol) in anhydrous THF (0.90 mL) at 0 °C under nitrogen. The solution turned yellow in colour. The reaction mixture was stirred for 2 hours at 0 °C prior to the addition of 2-[*N,N-bis*(trifluoromethanesulfonyl)-amino]-5-chloropyridine **172** (372 mg, 0.95 mmol) in one portion, turning the solution amber in colour. The reaction mixture was allowed to slowly warm to room temperature over 18 hours. The mixture was quenched with a saturated aqueous Na_2CO_3 solution (20 mL) and extracted with diethyl ether (2 × 20 mL), the organic extracts combined, dried over $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (petrol) to yield *triflate* **225** (210 mg, 51%) as a pale yellow oil. ν_{max} (NaCl)/cm^{-1} 3587, 3536, 3354, 2952, 1635, 1599, 1575, 1507, 1489, 1447, 1423, 1401, 1377, 1349, 1213, 1127, 1080, 1061, 1016, 1003, 930, 909, 860, 837, 807, 778, 754, 737, 692, 638, 649; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.91-1.02 (2H, m, CH_2Si), 1.58-1.66 (2H, m, *cyc*-$CH_2CH_2CH_2$), 1.67 (3H, s, $CH_3C{=}C$), 1.71-1.82 (1H, m, *cyc*-CH_2), 1.85 (3H, s, $ArCCH_3$), 2.23-2.31 (2H, m, *cyc*-CH_2), 2.34-2.47 (1H, m, *cyc*-CH_2), 3.73 (2H, app. t, *J* 7.9, OCH_2CH_2), 5.16 (2H, app. s, OCH_2O), 6.95 (1H, ddd, *J* 7.9, 7.2 and 1.5, Ar-*H*), 7.12 (1H, dd, *J* 8.3 and 1.5, Ar-*H*), 7.21 (1H, ddd, *J* 8.3, 7.2 and 1.5, Ar-*H*), 7.28 (1H, dd, *J* 7.9 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.4, 19.5, 20.5, 25.9, 33.6, 39.6, 44.5, 67.7, 94.4, 115.9, 119.1 (q, J_{CF} 318.9), 122.6, 127.0, 129.6, 130.1, 133.8, 150.2, 157.0.

Preparation of **6-(2-hydroxyphenol)-2,6-dimethylcyclohexen-1-yl trifluoromethanesulfonate, 226**



HCl (1M in H_2O, 1.00 mmol, 1.00 mL) was added to a solution of *triflate* **225** (100 mg, 0.21 mmol) in THF (0.30 mL) and the reaction mixture heated to 80 °C for 16 hours. The reaction was quenched with a saturated aqueous Na_2CO_3 solution (20 mL), extracted with diethyl ether (2 × 20 mL) and the organic extracts combined, dried over $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (5% diethyl ether:petrol) to yield *phenol* **226** (22 mg, 32%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3066, 2953, 1683, 1601, 1588, 1491, 1448, 1417, 1246, 1210, 1144, 1111, 1088, 1028, 1000, 909, 858, 838, 755, 606; δ_H (300 MHz, $CDCl_3$) 1.61-1.68 (2H, m, $CH_2CH_2CH_2$), 1.70 (3H, s, ArCCH_3), 1.71-1.85 (1H, m, CH_2), 1.89 (3H, s, CH_3C=C), 2.27-2.46 (3H, m, CH_2), 4.98 (1H, s (br), Ar-O*H*), 6.74 (1H, dd, *J* 7.9 and 1.2, Ar-*H*), 6.91 (1H, app. td, *J* 7.5 and 1.2, Ar-*H*), 7.15 (1H, ddd, *J* 7.9, 7.3 and 1.6, Ar-*H*), 7.26 (1H, dd, *J* 7.5 and 1.6, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 17.8, 18.9, 24.3, 32.2, 38.0, 42.8, 117.1, 118.9 (q, J_{CF} 320.2), 120.7, 128.0, 128.3, 128.6, 130.1, 147.8, 153.6.

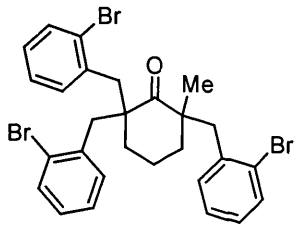
Preparation of **2-(2-bromobenzyl)-2-methylcyclohexanone, 233**



A solution of 2-methylcyclohexanone (800 mg, 7.14 mmol, 0.87 mL) in anhydrous DMF (1.50 mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 329 mg, 13.71 mmol) in anhydrous DMF (2.00 mL) at 0°C, under nitrogen, over a period of 20 minutes. The reaction mixture was allowed to stir at 0 °C for a further 30 minutes then allowed to warm to room temperature for one hour prior to the dropwise addition of diethylzinc (1M in hexanes, 7.14 mmol, 7.10 mL). The reaction mixture was heated to 50 °C for 2 hours prior to the dropwise addition of a solution of 2-bromobenzylbromide (2.140 g, 8.57 mmol) in anhydrous DMF (1.50 mL) and the

temperature sustained at 50 °C over 18 hours. After cooling, the mixture was quenched with a saturated aqueous NH_4Cl solution (30 mL), extracted with diethyl ether (2 × 30 mL) and the organic extracts combined, washed with brine (10 mL), dried over $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (2% diethyl ether:petrol) to yield *ketone* **233** (800 mg, 40%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3061, 2934, 2864, 1705, 1565, 1469, 1436, 1377, 1337, 1281, 1124, 1073, 1048, 1024, 755, 733, 659; δ_H (300 MHz, $CDCl_3$) 1.11 (3H, s, CC*H*$_3$), 1.63-1.94 (6H, m, *cyc*-C*H*$_2$), 2.51 (2H, app. t, *J* 6.6, C*H*$_2$CO), 3.16 (2H, AB q, ν_A 3.11 and ν_B 3.20, *J* 14.2, Ar-C*H*$_2$), 7.00-7.08 (1H, m, Ar-*H*), 7.16-7.20 (2H, m, Ar-*H*), 7.53 (1H, d, *J* 7.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 21.1, 22.8, 27.2, 38.5, 38.8, 41.3, 50.2, 126.3, 126.9, 127.8, 132.1, 133.0, 137.9, 215.1; *m/z* LRMS (EI$^+$) 283 [M+H:^{81}Br]$^+$ (95%), 281 [M+H:^{79}Br]$^+$ (100%), 267 [M+H-O:^{81}Br]$^+$ (42%), 265 [M-O:^{79}Br]$^+$ (52%); (CI$^+$, NH_3) 300 [M+NH_4:^{81}Br]$^+$, 298 [M+NH_4:^{79}Br]$^+$; HRMS (ES$^+$) calc. for $C_{14}H_{21}BrNO$: 298.0801 [M+NH_4:^{79}Br]$^+$; found: 298.0802 [M+NH_4:^{79}Br]$^+$.

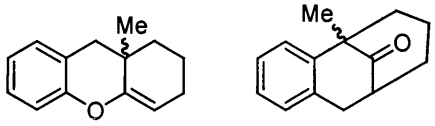
Preparation of **2-(2-bromobenzyl)-2,6-*bis*-(2-bromobenzyl)-6-methylcyclohexanone, 233a**



When the above reaction was carried out in the absence of diethylzinc, a *polyalkylated species* **233a** was recovered in 50% yield as white spikey crystals: mp 101-103°C. ν_{max} (KBr)/cm^{-1} 2925, 2855, 1687, 1562, 1459, 1432, 1377, 1022, 758, 740; δ_H (300 MHz, $CDCl_3$) 1.10 (3H, s, CC*H*$_3$), 1.30-1.43 (1H, m, *cyc*-C*H*$_2$), 1.63-1.89 (5H, m, *cyc*-C*H*$_2$), 2.96-3.20 (4H, m, Ar-C*H*$_2$), 3.44 (2H, AB q, ν_A 3.41 and ν_B 3.47, *J* 11.5, Ar-C*H*$_2$CCH$_3$), 7.02-7.10 (3H, m, Ar-*H*), 7.15-7.26 (6H, m, Ar-*H*), 7.51-7.56 (3H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 16.8, 24.8, 28.7, 33.2, 40.8, 41.4, 42.3, 49.2, 55.6, 126.1, 126.4, 126.4, 126.5, 126.6, 126.7, 127.5, 127.6, 127.7, 132.1, 132.3, 132.4, 132.6, 132.6, 137.1, 137.2, 218.3; *m/z* LRMS (CI$^+$, NH_3) 640 [M+NH_4:^{81}Br]$^+$, 638 [M+NH_4:$^{79/81/81}$Br]$^+$, 636 [M+NH_4:$^{79/79/81}$Br]$^+$, 634 [M+NH_4:^{79}Br]$^+$, 470 [M-BrOC$_4$H$_6$:^{81}Br]$^+$, 468 [M-BrOC$_4$H$_6$:$^{79/81}$Br]$^+$, 466 [M-BrOC$_4$H$_6$:^{79}Br]$^+$, 388 [M-

$Br_2OC_4H_8$:^{81}Br]$^+$, 386 [M-$Br_2OC_4H_8$:^{79}Br]$^+$, 300 [M-$Br_2OC_{10}H_{24}$:^{81}Br]$^+$, 298 [M-$Br_2OC_{10}H_{24}$:^{79}Br]$^+$; HRMS (CI^-, NH_3) calc. for $C_{28}H_{26}OBr_3$: 614.9539 [M-H:^{79}Br]$^-$; found: 614.9535 [M-H:^{79}Br]$^-$; $C_{28}H_{27}OBr_3$ requires C 54.31, H 4.39%, found C 54.50, 4.43%.

Preparation of **9a-methyl-2,3,9,9a-tetrahydro-1*H*-xanthene, 234; 9-methyl-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-13-one, 241**



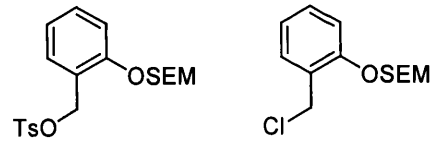
Cesium carbonate (87 mg, 0.27 mmol) was added to a flask charged with $Pd_2(dba)_3$ (4 mg, 0.01 mmol) and DPEphos (6 mg, 0.01 mmol) under nitrogen and the reagents suspended in anhydrous dioxane (0.20 mL). *Ketone* **233** (50 mg, 0.178 mmol) was added and the reaction heated to 100 °C for 20 hours. After cooling, the reaction mixture was diluted with diethyl ether (*ca.* 10 mL), filtered through celite and reduced *in vacuo*. The residue was purified *via* flash column chromatography (petrol) and recrystallised from diethyl ether to yield *C-arylated cyclised product* **241** (26 mg, 73%) as a white crystalline solid: mp 53-55°C. ν_{max} (KBr)/cm^{-1} 3063, 3021, 2965, 2929, 1720, 1490, 1455, 1444, 1378, 1336, 1276, 1136, 1076, 756, 721; δ_H (300 MHz, $CDCl_3$) 1.14 (3H, s, CC*H*$_3$), 1.61 (1H, tt, *J* 13.0 and 4.2, C*H*$_2$), 1.67-1.81 (2H, m, C*H*$_2$), 1.92-2.02 (2H, m, C*H*$_2$), 2.08 (1H, tt, *J* 13.0 and 4.2, C*H*$_2$), 3.17 (2H, AB q, ν_A 3.09 and ν_B 3.25, *J* 17.7, Ar-C*H*$_2$), 3.54 (1H, app. t, *J* 3.4, C=C*H*), 6.94-7.00 (1H, m, Ar-*H*), 7.06-7.12 (1H, m, Ar-*H*), 7.14-7.20 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 18.0, 23.8, 38.0, 45.2, 46.2, 46.5, 52.8, 126.6, 126.7, 127.8, 136.0, 138.6, 216.2; *m/z* LRMS (EI$^+$) 200 [M]$^+$ (73%), 172 [M-CO]$^+$ (22%), 157 [M-C_2H_3O]$^+$ (27%), 143 [M-C_3H_6O]$^+$ (65%), 129 [M-C_4H_8O]$^+$ (72%); (CI^+, NH_3) 218 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{14}H_{20}NO$: 201.1274 [M+NH_4]$^+$; found: 201.1273 [M+NH_4]$^+$.

When the above reaction was carried out using KHMDS (0.5M in toluene, 0.27 mmol, 0.54 mL) as base, the desired *O-arylated cyclised product* **234** was obtained, albeit in low conversion (22% conv.). Characteristic peaks (impure reaction mixture) δ_H (300 MHz, $CDCl_3$) 2.61 (2H, AB q, ν_A 2.43 and ν_B 2.66, *J* 15.5, Ar-C*H*$_2$), 5.18 (1H, t, *J* 3.9, C=C*H*).

Preparation of **[2-(2-trimethylsilanylethoxymethoxy)-phenyl]-methanol, 252a; 2-(2-Trimethylsilanylethoxymethoxymethyl)-phenol, 252b**

Triethylamine (3.26 g, 32.20 mmol, 4.49 mL) was added dropwise to a solution of 2-hydroxymethyl-phenol (2.00 g, 16.11 mmol) in anhydrous THF (10.00 mL) at 0 °C over 30 minutes. The reaction mixture was stirred for 30 minutes prior to the dropwise addition of trimethylsilylethoxymethyl chloride (2.95 g, 17.72 mmol, 3.14 mL). The reaction mixture was allowed to warm to room temperature and continued stirring for a further 2 hours until completion. The mixture was quenched with water (10 mL), extracted with diethyl ether (2 × 20 mL) and the organic extracts combined, dried with $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (50% diethyl ether:petrol) to yield *protected phenol* **252a** (984 mg, 24%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3405, 3066, 3043, 2954, 2896, 1604, 1590, 1491, 1457, 1411, 1381, 1282, 1249, 1228, 1192, 1146, 1089, 1045, 997, 937, 919, 834, 753, 694; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, Si(C*H*$_3$)$_3$), 0.91-1.01 (2H, m, C*H*$_2$Si), 2.33 (1H, t, *J* 6.6, ArCH$_2$O*H*), 3.72-3.80 (2H, m, OC*H*$_2$CH$_2$), 4.69 (2H, d, *J* 6.8, Ar-C*H*$_2$OH), 5.28 (2H, s, OC*H*$_2$O), 7.00 (1H, td, *J* 7.3 and 1.1, Ar-*H*), 7.13 (1H, dd, *J* 8.3 and 1.1, Ar-*H*), 7.22-7.33 (2H, m, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.5, 63.4, 68.0, 94.6, 115.7, 123.3, 130.3, 130.5, 131.4, 156.9. *Protected hydroxymethyl phenol* **252b** (324 mg, 8%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3394, 3042, 2953, 2895, 1612, 1589, 1491, 1457, 1408, 1377, 1250, 1185, 1153, 1107, 1057, 1030, 938, 859, 835, 753, 695; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, Si(C*H*$_3$)$_3$), 0.88-1.01 (2H, m, C*H*$_2$Si), 3.58-3.71 (2H, m, OC*H*$_2$CH$_2$), 4.74 (2H, s, Ar-C*H*$_2$), 4.75 (2H, m, OC*H*$_2$O), 6.84 (1H, td, *J* 7.3 and 1.1, Ar-*H*), 6.89 (1H, dd, *J* 8.4 and 1.3, Ar-*H*), 7.07 (1H, dd, *J* 7.5 and 1.5, Ar-*H*), 7.21 (1H, td, *J* 7.5 and 1.5, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.5, 67.5, 69.5, 95.4, 118.2, 121.5, 123.8, 130.5, 131.2, 157.5.

Preparation of **2-(2-trimethylsilanylethoxymethoxy)-benzyl toluene-4-sulfonate, 253; [2-(2-chloromethylphenoxymethoxy)-ethyl]-trimethylsilane, 253a**



Triethylamine (0.39 g, 3.89 mmol, 0.54 mL) was added dropwise to a solution of [2-(2-trimethylsilanylethoxymethoxy)-phenyl]-methanol **252a** (900 mg, 3.54 mmol) in anhydrous DCM (4.00 mL) at 0 °C over 30 minutes. The reaction mixture was stirred for one hour prior to the portion-wise addition of *p*-toluenesulfonyl chloride (0.74 g, 3.89 mmol). The reaction mixture was allowed to warm to room temperature and continued stirring over 18 hours. The mixture was quenched with water (10 mL), extracted with diethyl ether (2 × 20 mL) and the organic extracts combined, dried with $MgSO_4$ and reduced *in vacuo*. The resulting residue was purified *via* flash column chromatography (10% diethyl ether:petrol) to yield *diprotected phenol* **253** (110 mg, 8%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3396, 3067, 2962, 2905, 1598, 1490, 1452, 1411, 1379, 1262, 1194, 1181, 1155, 1091, 1027, 941, 862, 803, 709, 701; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, Si(CH_3)$_3$), 0.87-0.96 (2H, m, CH_2Si), 2.44 (3H, s, Ar-CH_3), 3.56-3.64 (2H, m, OCH_2CH_2), 4.45 (2H, s, Ar-CH_2O), 4.64 (2H, s, OCH_2O), 7.01 (1H, app. dd, *J* 7.5 and 1.5, Ar-*H*), 7.17-7.28 (2H, m, Ar-*H*), 7.31 (2H, app. d, *J* 7.9, Ar-*H*), 7.74 (2H, app. dt, *J* 8.3 and 1.9, Ar-*H*), 7.44 (1H, app. dd, *J* 7.3 and 2.3, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.5, 23.1, 65.2, 66.7, 95.9, 123.6, 128.5, 129.9, 130.0, 131.0, 131.2, 133.3, 134.3, 146.8, 148.7. *Chlorinated* **253b** (130 mg, 14%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3046, 2954, 2898, 1730, 1603, 1591, 1493, 1458, 1440, 1411, 1382, 1289, 1263, 1250, 1234, 1196, 1149, 1090, 1046, 998, 938, 918, 859, 836, 754, 693, 674; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, Si(CH_3)$_3$), 0.93-1.00 (2H, m, CH_2Si), 3.76-3.83 (2H, m, OCH_2CH_2), 4.67 (2H, s, OCH_2O), 5.31 (2H, s, Ar-CH_2Cl), 6.99 (1H, td, *J* 7.3 and 1.1, Ar-*H*), 7.14 (1H, dd, *J* 8.3 and 1.1, Ar-*H*), 7.26-7.32 (1H, m, Ar-*H*), 7.36 (1H, dd, *J* 7.5 and 1.9, Ar-*H*); δ_C (75 MHz, $CDCl_3$) 0.0, 19.5, 43.2, 67.9, 94.1, 115.7, 123.0, 127.9, 131.5, 132.0, 156.6.

7.3 References

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Appendix

Computational Report

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Computational details

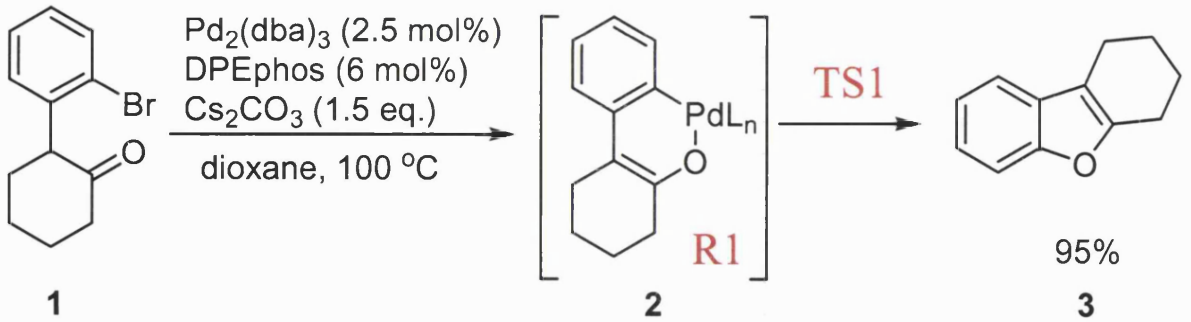
- All the calculations were carried out using Spartan02 package.

- Geometry optimisations were carried out using the semi-empirical approach PM3™.

- All stationary points have been fully optimised and characterised by harmonic analysis. For each transition structure (TS), one imaginary frequency was found in the diagonalised Hessian matrix, and the corresponding vibrations was found to be associated with the nuclear motion perpendicular to the molecular plane.

- No solvent effects were taken into account.

Pd-catalysed enolate cyclisation



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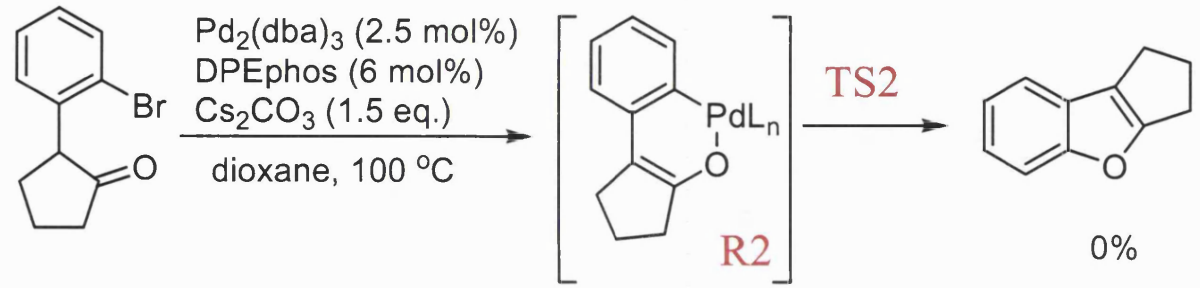

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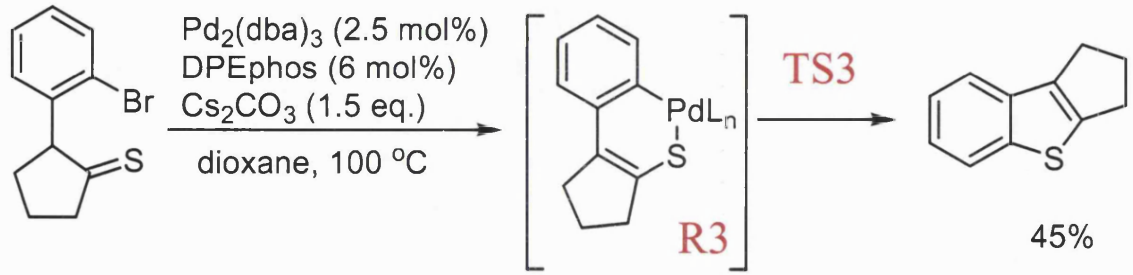
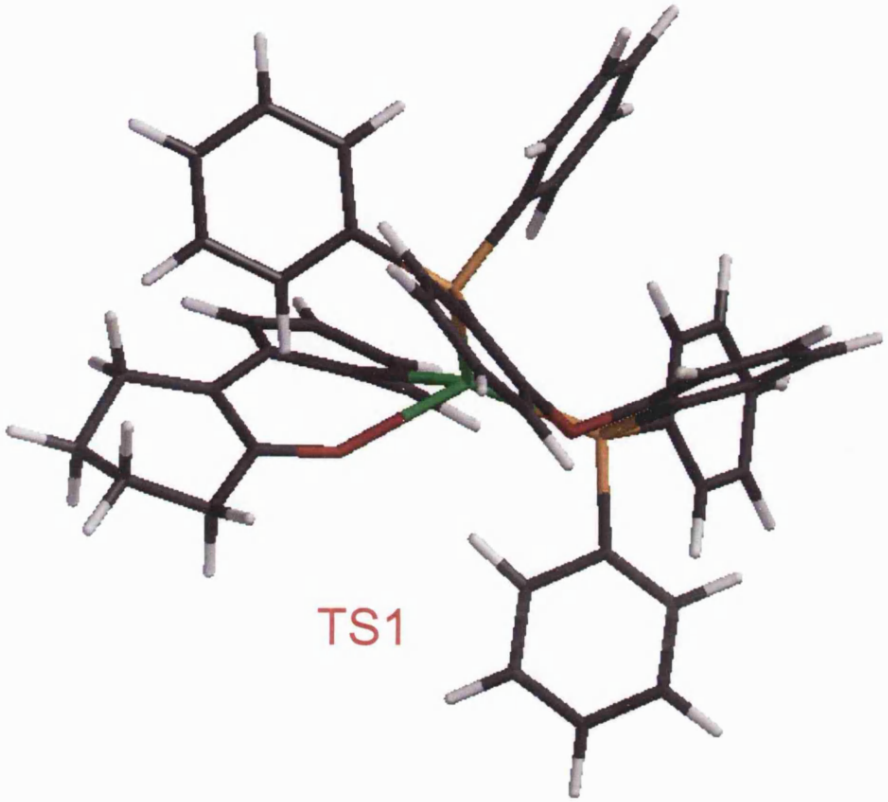


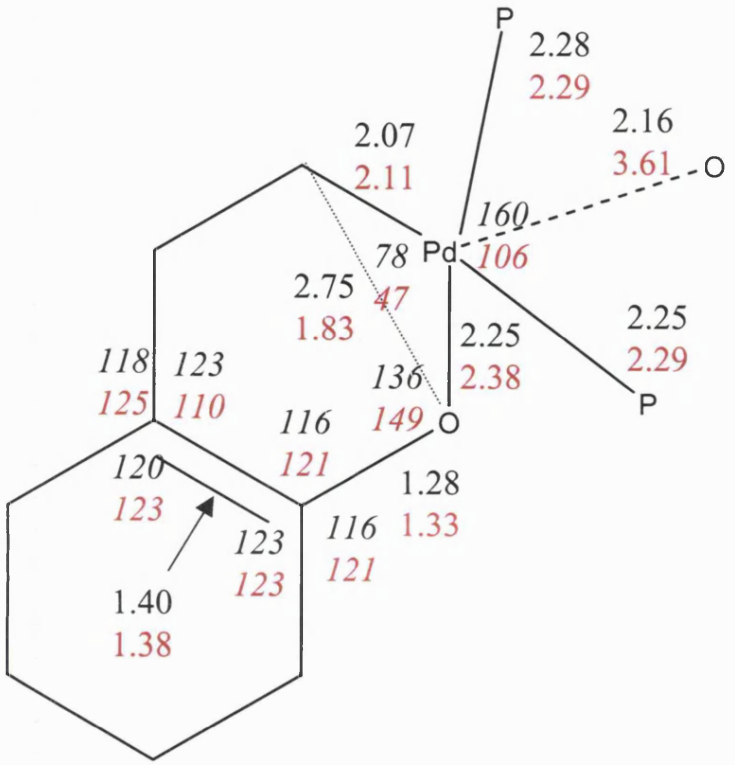
7 8 9

Why?

O-nucleophile 6 membered-ring

Reactant
TS

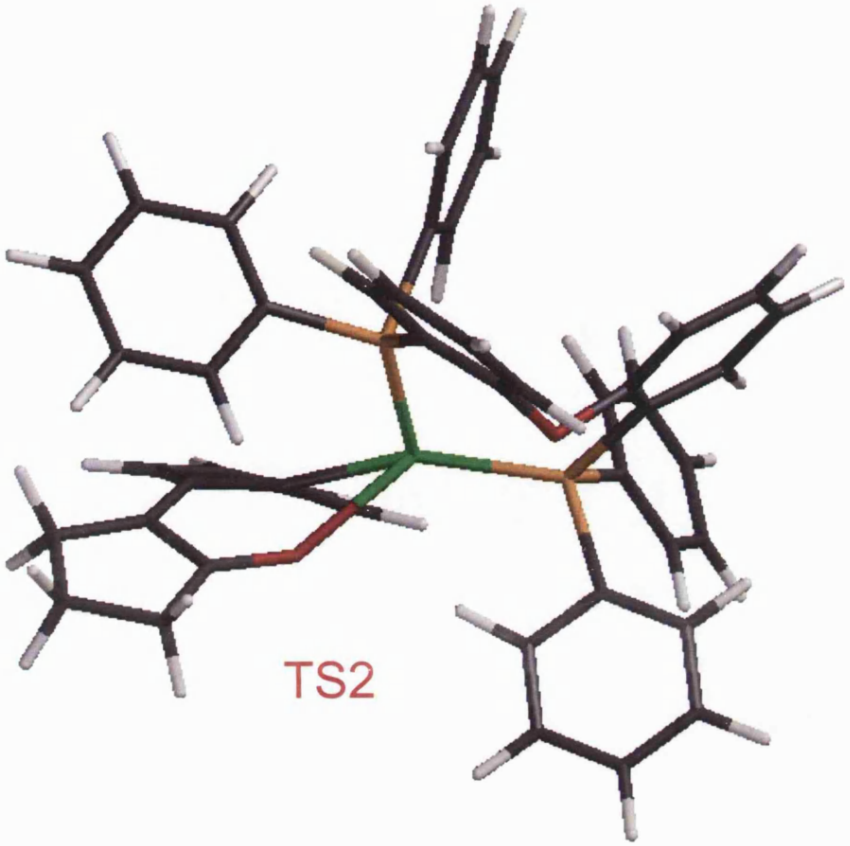


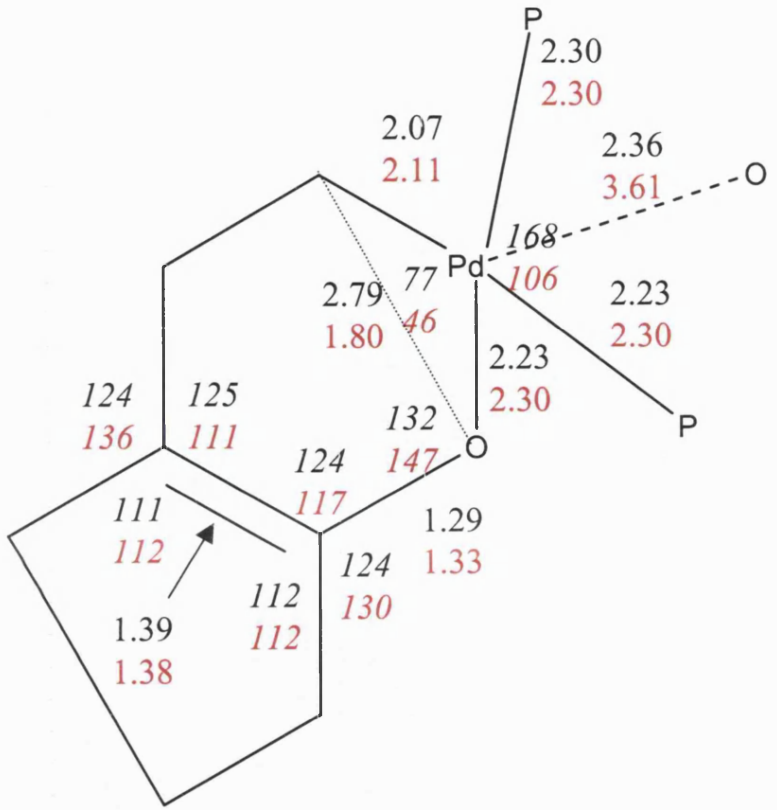


ΔE_{act}= 23 kcal/mol

w(COPdC)= 14
-54

O-nucleophile 5 membered-ring

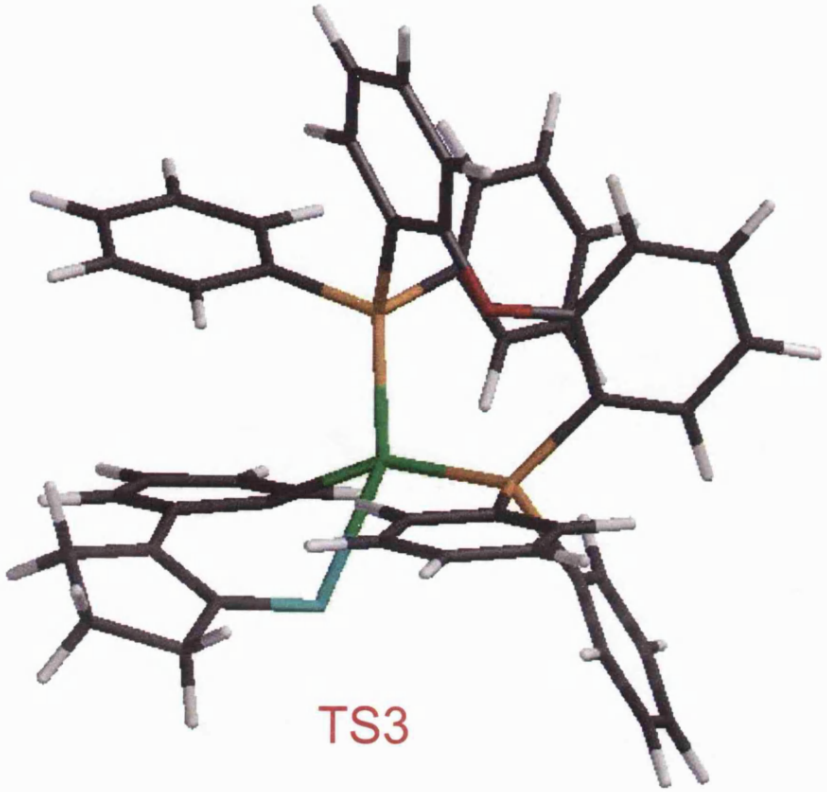


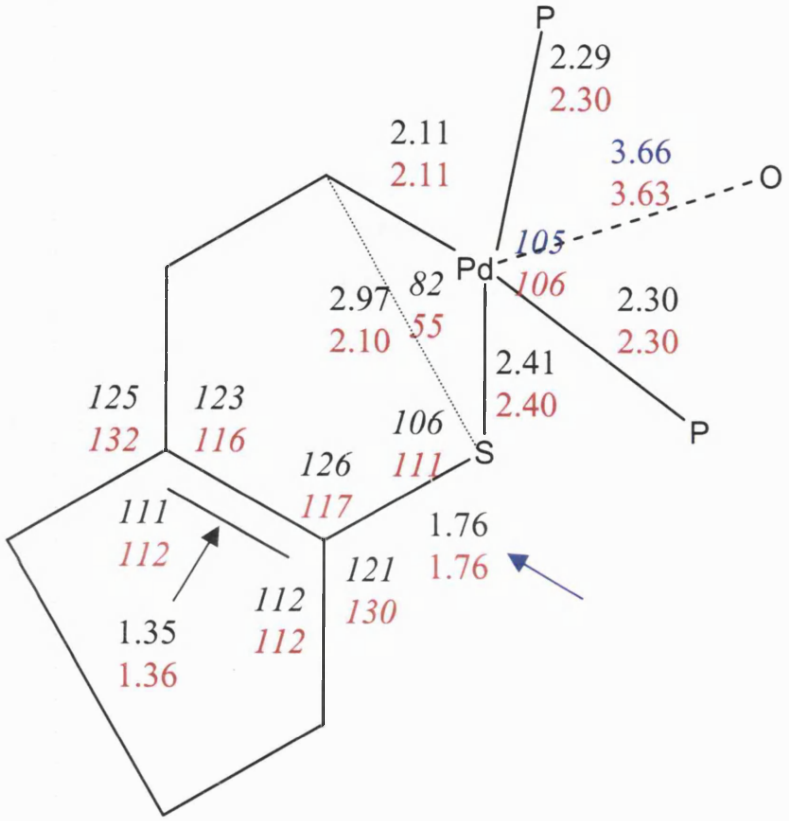


ΔE_{act}= 37 kcal/mol

w(COPdC)= 13
-54

S-nucleophile 5 membered-ring





ΔE_{act}= 29 kcal/mol

w(COPdC)= -47
-68

Conclusions

Preliminary calculations at PM3 level showed that the experimental outcome can be explained assuming as the C-O(S) bond formation is the rate-determining step. In this work only this kinetic step is considered.

It was found that the R1 (6 member) reacts with good yields because the activation barrier is relatively low (~20 kcal/mo)l. Instead, the cyclisation process for R2 (5 member) is really unlikely (~40 kcal/mol). This reason is because of the geometric constrains that this TS is bound to.

Interestingly, the S-enolate reactant R3 is very similar to the following transition structure, mainly thanks to the long distance C-S, modifying completely the structural pattern observed for O-analogues (see blue-highlights). The activation barrier is intermediate (30 kcal/mol) and it is in line with the experimentally found conversion.